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RECENT ADVANCES IN THE TREATMENT OF BURNS

R. I. HARRIS, M.C., M.B., F.R.C.S.(C)

The infinitely complex problem of burns (their pathology and treatment), has become of greater importance than ever before because of the number of burn casualties which are occurring in this war. Important as is the burn problem in civil practise, it is immensely greater in modern war. Motorized equipment, oil burning ships and incendiary bombs have caused enormous numbers of burns of every variety and degree of severity, complicated by many other forms of injury and occurring under the most adverse circumstances. Naval action often results in burns from exploding shells and powder charges, or from the ignition of fuel oil on the surface of the sea. At Pearl Harbour 40% of the naval casualties were burns. Airplane combat often ignites fuel tanks. The most distinctive injury in the airforce is a burn of the hands and face. Motorized army forces and armoured forces sustain many burns because of the quantity of gasoline they handle and use. In Lybia, 27% of the *battle* casualties of the armoured forces were burns. It is small wonder that the exigencies of war have stimulated an immense amount of research into problems related to burns.

In order to understand the significance of these researches it is well to remind ourselves of the complexity of the problem. Though burns are merely a special form of wound involving the skin, they initiate a train of physiological changes of the most profound importance, and of a severity out of all proportion to the area

of skin involved. Large areas of skin can be removed by surgery without causing any serious disturbance. Damage by heat of an equal area causes serious, often fatal consequences.

The seriousness of the burn problem is due to three grave complications which occur when the skin has been damaged by heat. First, is the enormous loss of plasma from the circulating blood. It exudes through damaged capillaries into tissue spaces and from thence through the skin into the blisters. This plasma loss is so great as to diminish the amount of circulating blood often to a dangerous degree and hence give rise to surgical shock. Second, there probably arise, from the disintegration of burned skin, certain toxic products which cause profound damage to parenchymal organs. The evidence for this is by no means indisputable but there is much clinical experience to support it. Third, so large an extent of damaged skin almost inevitably becomes infected and when it does the danger to life is great.

We may simplify the problem for the sake of clarity by saying that burns present problems in five phases as follows.

1. *Shock* (both primary and secondary). The great and painful injury caused by a burn often initiates primary or neurogenic shock. This is fairly easily controlled by morphine for the relief of pain. A much more serious problem is the secondary shock which develops a few hours after the burn and is due to the immense amount of plasma lost in the burn blisters and into the tissues about the burn. It manifests itself by the usual evidences of shock; haemoconcentration, cold extremities, rapid pulse, pallor, sweating, thirst and low blood pressure.

2. *Toxaemia.* When surgical shock has been controlled by adequate measures there ensues a period characterized by a clearly defined clinical picture which is thought by many to be due to a specific burn toxin produced from the burned skin as the result of its disintegration by enzyme reaction. It commences about the end of the second day and lasts for four or five days if the patient survives. The symptoms are more marked and more clearly defined in children than in adults. They are high fever (in contrast to the subnormal temperature of shock) vomiting, drowsiness, muscular twitchings and convulsions. In this period occur serious focal necrosis of parenchymal organs such as liver, kidney and duodenum (Curling's ulcer). The evidence that all this damage is due to a specific burn toxin unfortunately is meagre. No one has ever been able to isolate such a toxin though Bruce Robertson and Gladys Boyd(1) of this city thought they had done so many years ago. Drinker(2) in recent work has advanced some evidence which may be significant. The toxin theory is a useful working hypothesis until such time as we are able to determine more clearly the nature of this serious and highly fatal phase of the burn problem.

3. *Sepsis.* Sooner or later the burn is likely to be invaded by pathogenic organisms. It is nearly impossible to prevent contamination by skin organisms such as staphylococci or by organisms from the respiratory tract such as haemolytic streptococci. Infection usually does not manifest itself until near the end of the first week. The evidences of its existence then are septic temperature, purulent discharge from the burned area and inflammatory reaction in the skin about the burn. Not infrequently the blood stream is invaded. Uncommon infections sometimes occur such as infection with scarlet fever streptococci resulting in surgical

scarlet fever, or infection with bacillus pyocyanines.

4. *Wound Repair.* If the patient survives shock, toxaemia and sepsis the necrotic skin ultimately separates and the problem of wound healing commences.

The magnitude of this problem is dependant upon the depth of the burn and the degree of sepsis. If the complete thickness of the skin has been destroyed the wound can only heal by ingrowth of epithelium from the margins unless skin-grafting is used successfully. If but part of the skin is burned, healing will be more rapid. Sepsis delays healing; sometimes it even destroys new epithelium. The problem of wound healing end when all of the burned area is completely recovered with epithelium.

5. *Scar Contracture.* In the process of wound healing a greater or less amount of scar tissue is formed. As it becomes more mature it contracts with a degree of force which depends upon the amount of scar. In the neighbourhood of joints this contracting scar can cause deformities. In lax tissues, especially those of the face it can cause serious disfigurement. After the lapse of time the contraction ceases and the scars with their resulting deformities and disfigurements reach a stage of permanence. During this period much can be done by plastic surgery to prevent contractures or correct them when they have arisen.

* * *

Under the stimulus of war needs much new research into burn pathology and burn treatment is being conducted. The following summary gives some idea of what is being accomplished in this field.

1. Research Related to the Pathology of Burns

A. *Drinker and Glen*(2), Boston, have conducted an extensive study into the local pathology of burns and the possible existence of a burn toxin. The experiments utilized a standardized form of burn injury and are based upon Drinker's well known knowledge and skill in the study of lymph flow(3). Summarized their findings are:

Lymph Drainage Experiments. A burn resulted in an immediate and great increase in the quantity of lymph flow from the burned area and a great increase in the protein content of the lymph. The quality of the lymph in changed in other respects. It contains red blood cells and haemoglobin and has the power to cause haemolysis when it reaches the circulation. This observation indicates the severity of the capillary damage caused by the burn and the quantity of plasma which leaks through the damaged capillary walls.

Toxic factors produced at the site of burn. There is considerable evidence pointing to the existence of a toxic factor. The presence of haemoglobin has been mentioned above as well as the property of the lymph to cause haemolysis. If the animal is heparinized there is no coagulation of the lymph in the tissue spaces, consequently more of its flows back into the circulation. Death occurs more frequently in heparinized than in non-heparinized animals and with less local swelling. Intense changes occur in the duodenum of 70% of heparinized animals as against 40% of non-heparinized animals. Severe liver changes with central necrosis occur in 10% of the burned animals.

B. *Beecher,* Boston. Studies in the control of fluid loss in burns(4) has demonstrated that the administration of barbiturates (nembutal) immediately after the burn results in greatly diminished fluid loss at the site of the burn (20 to

35% less loss). Translated into terms comparable to the bulk of an average man this would be the equivalent of 600 c.c. of plasma. The flow of lymph from the burned area was 50% less in nebutalized dogs than in controls. The mechanism of this diminished plasma loss is not known but it is of considerable practical importance.

C. Kabat and Levine(5) call attention to to the effect of heat upon blood and upon plasma. A moderate degree of heat causes precipitation of fibrinogen in the plasma and this can cause rapid death from multiple minute pulmonary emboli. The work suggests two possibilites. (1) During the time when the skin is being burned the blood circulating through it may be heated to the critical point and precipitation of fibrinogen in the plasma with pulmonary embolism may cause early death. (2) If plasma from a bank is heated too rapidly or to too high a level precipitation may occur with harm to the patient.

D. *Cope*(6) developing an idea of Colebrook's that the skin has powers of bacteriostasis (probably residing in the sweat) demonstrates that bleb fluid is mostly sterile. From this he argues that extensive cleansing of the burn before dressing is not necessary. He demonstrates also that the bleb fluid contains as much sulphonamide as may be present in the blood stream at the time the blebs form. Hence the early administration of sulphonamides, intravenously if necessary, will result in the formation of blebs containing a reasonable concentration of sulphonamide. Cope's ideas were sufficiently advanced and supported by sufficient evidence to justify the exclusive use of this method at the Massachusetts General Hospital in the treatment of the burns from the Cocoanut Grove Disaster of November 28, 1942. The simplification of treatment which resulted from simple dressing of the wound with a bland ointment without preliminary cleansing or debridement enabled the staff of that hospital to treat adequately thirty-nine badly burned patients within three hours.

2. Research Related to the Tanning Method of Treating Burns

Davidson's introduction of tannic acid in 1925 marked a new era in the treatment of burns. It was based upon a broad conception of the pathology of burns and attacked the basic problems in a novel and effective manner. Improved results followed its use so that from 1925 until almost the present time it has dominated the field of treatment. Perhaps the most important thing achieved by Davidson was to attract the attention of the Medical World to the complexity of the burn problem and to the necessity of dealing with burns on a much broader basis than as local wounds.

Despite the success of Davidson's method it has long been admitted that there are certain defects in the tannic acid treatment. Its great merits, however, have overwhelmed its defects, at least until recent years. Seventeen years have now passed since Davidson first introduced it. In that time we have learned new and efficient methods of treating shock and infection so that the problem of saving the life of a burned patient is less formidable today than it was then, grave though it still is. This general improvement in burn treatment has naturally thrown the shortcomings of tannic acid into more prominence and has led to speculation regarding the possibility of improvement upon the tannic acid treatment of burns. The recent discovery by Wells of a new and harmful effect of tannic acid

has brought the whole problem into sharp focus.

Shortcomings of the Tannic Acid Treatment of Burns

A. There have always been those who stated that tannic acid not only tanned the skin which had been killed by heat but also tanned and killed a certain amount of the living skin beneath the dead epithelium and so might convert a partial thickness burn into a full thickness burn. There is, perhaps, some doubt of the accuracy of this statement. Certainly no clear proof of it has ever been produced. None the less many surgeons are strongly of the opinion that such destruction of the underlying living epithelium can occur and they would welcome a better tanning agent than tannic acid or even an entirely new method of treatment. Though the fear of this action of tannic acid may be groundless or grossly exaggerated there is no doubt that tannic acid does *delay healing* beneath the eschar it produces. In partial thickness burns the ingrowing epithelium has some difficulty in insinuating itself between the eschar and the underlying dermis, and in full thickness burns healing does not begin until the eschar has separated. This may be three or four weeks.

B. If infection occurs beneath the tanned burn it may be troublesome or even dangerous because of imperfect drainage. Such a complication (infection pent up beneath tan) does not occur very frequently; when it does occur an alert surgeon can handle it satisfactorily by removing the tan to provide drainage. Only rarely does serious infection arise; but one must admit that occasionally this is the case.

C. A much more serious criticism of tannic acid is that suggested by D. B. Wells(7). He called attention to the frequent presence of severe liver necrosis in fatal burns treated with tannic acid, and suggested that this might be due to tannic acid, since the experimental injection of tannic acid subcutaneously and intraperitoneally produced similar liver necrosis.

Well's suggestion has aroused widespread interest and concern. It is not possible yet to say whether or not it is correct. There is a good deal of evidence which strongly suggests that he may be correct. So far no one has been able to produce evidence of liver necrosis in a fatal burn not treated by tannic acid. A review of the records of the Hospital for Sick Children in Toronto yields twenty cases who died prior to the use of tannic acid, whose liver sections are still available for study. Thirteen of these died within forty-eight hours and hence before liver changes occur. The remaining seven, while they show liver changes in the form of fatty infiltration, do *not* show the characteristic central necrosis of the liver lobule which has been described by several workers (8, 9), and which Wells suggests may be due to tannic acid poisoning. Of forty-one cases who died after treatment by tannic acid, twenty-seven died on the third to nineteenth day and of these, twenty-four showed liver necrosis. Failure so far to find this necrosis in fatal burn untreated by tannic acid, may be because few burns are treated other than with tannic acid. This point should be soon cleared up. It is certain, however, that the same kind of necrosis can be caused by the subcutaneous injection of tannic acid (rather than its surface application as in a burn). Hartman (Detroit) is demonstrating that nearly all escharotics when injected subcutaneously or intraperitoneally will cause the same liver necrosis. In one hundred animals

burned and tanned there was no liver necrosis. This suggests that the liver necrosis they produce is due to a common factor, which might be the toxic products of tissue damage and hence comparable to the tissue damage caused by the burn. He has not been able to produce the characteristic liver necrosis by tanning burns in dogs. The whole problem of the possible toxicity to the liver of tannic acid is as yet unanswered. Much work is being done upon it. Many surgeons regard Wells' suggestion as a serious criticism of tannic acid treatment though Wells himself does not.

D. A minor objection to tannic acid is the stiffness and brittleness of the eschar. This results in discomfort to the patient if the film is on parts which are sensitive and actively mobile such as fingers or face. In these critical areas tannic acid should not be used.

E. The tannic acid eschar tends to shrink as it tans the dead skin. Hence if the tan completely surrounds a small structure such as finger or forearm it might interfere with the circulation. This danger certainly is real if rare. It can be dealt with by splitting the constricting agent (the tan) as one would deal with any other circulatory disturbance produced by constriction. In two thousand burns treated at the Children's Hospital in Toronto none have lost digits from this cause though two have lost digits who were not tanned.

F. The first aid use of tannic acid in the form of a water soluble jelly is apparently far different and much less satisfactory than its use as a spray. The cause for this is not clear but perhaps the greatly prolonged time which elapses before the tan becomes dry may be a factor. Wilson's report of burns in the Lybian campaign indicates how strongly he has been impressed with the dangers of tannic acid jellies. Also its use as a first aid measure interferes with subsequent debridement.

G. Under the difficulties of supply imposed by war conditions it has been feared that the quantity of tannic acid available might be insufficient to permit us to plan the treatment of war burns by this method. Tannic acid is derived from nut-galls which have come from the East Indies. This source of supply is stopped and we are dependent upon the stocks in hand. In spite of this difficulty and the wide use of tannic acid in industry (brewing, leather manufacturers, etc.) I am assured by W.P.B. that the supplies in U.S.A. are ample for any medical needs for a long time to come.

These objections to and shortcomings of the tannic acid treatment of burns loom large in the minds of many surgeons today. It is my impression that too much emphasis is placed upon the shortcomings and too little attention is paid to the great merits of tannic acid (the sealing of the wound against the transudate of plasma, the diminution of toxaemia, the reduction of infection; the ease and comfort of the patient and especially the lowered mortality). But perhaps the time has come to improve the tannic acid treatment. Many people think so and much of the work upon burns which is under way today is directed towards this end.

3. Research Designed to Improve the Treatment of Burns by the Tanning Method.

A. *The production of a superior eschar by modifying the pH of the tanning solution.* The knowledge of tanning chemists has been drawn upon by Seegar (10) and enlarged upon by Fox. If the pH of the tanning solution is in the neighbourhood

of 7.5, the eschar produced is like commercial leather instead of being like dry rawhide; i.e. it is tough but flexible. In effect this means tanning with tannates and not tannic acid. Fox has used sodium sulphathiozole to neutralize the tannic acid and so has combined a sulphonamide with the tanning solution. This method has merit and should be given a trial. Certainly a tough flexible tan which will not break or crack open would be superior to the usual dense hard eschar.

B. *Substitutes for tannic acid.* The possible shortage of tannic acid has led to some investigation of other tanning agents. Of these only one is of any possible importance, viz., quebracho, a South American vegetable tanning extract. It tans quickly. It is perhaps more powerful than tannic acid. The tan shrinks a great deal. It is unlikely to be used unless the supply of tannic acid is exhausted.

C. *Coagulation of the burn by agents other than those commonly used for tanning.* This is the most promising activity in this field of research and the best piece of work in it is being carried out by Isadore Gersh(11) of Johns Hopkins. He has devised methods of testing the relative efficiency of coagulating agents and measuring their pain producing effect and determining what factors control the coagulating activity of the agent. His use of cellulose sulphate gives promise of a new tanning agent of great efficiency and without the objections of tannic acid. It is about ten times more powerful in tanning effect than tannic acid solution, and the depth of the tan can be regulated precisely.

D. *Attempts to remove the tannic acid eschar more rapidly by the use of enzymes.* Dr. Joseph Beard(12) of Duke University has been using enzymes to digest off the tan when separation has begun. His best solution to date is papeine 2%, cystine 0.4% and salicylate 8%. With this the tan may be digested off with fair rapidity but the action is not perfect. In any case to clip off the partially separated film with scissors would seem more rapid and efficient.

E. A great amount of research has been stimulated by Wells' paper. As yet the results are conflicting. Irwin and Sellars(13) have not been able to confirm Wells' findings. Hartman(14), Detroit, has carried out the most extensive work. He has not been able to cause liver necrosis in burned dogs treated by tannic acid but when tannic acid or many other escharotics are injected subcutaneously there is produced in every case the type of central liver necrosis described by Wells. This common effect of various different escharotics suggests that their effect is not produced directly but is caused by toxic products from the tissue necrosis they cause. If this be correct the liver necrosis of burns is due to the tissue damage caused by the burn rather than to the action of tannic acid. It should soon be possible to determine whether Wells' statement is or is not correct and to modify our treatment accordingly.

4. Research Concerned with the Production of Films of Various Types, Some of Which Incorporate Sulphonamides.

Many attempts are being made to devise films of plastic and adhesive material which, when applied to a burned area, will (1) seal the burn and prevent the exudate of plasma; (2) securely cover the burn and protect it from bacterial contamination; (3) hold in intimate contact with the burn whatever chemical might be judged of value; (4) in some cases to

hold incorporated in the film sulphonamides in various forms. The general principle seems to be an attempt to secure some of the merits of tannic acid films plus several advantages peculiar to the films themselves. None have as yet been very satisfactory. The following are some of the many which have been devised.

(a) The polyvinyl alcohol films of Dr. Sievertz. This is a gummy solution containing sulphonamides and an antiseptic. It can be applied as a paste. It dries into a flexible transparent film in an hour or two. Plasma collects beneath the film and finally dissolves it since it is water soluble. It does not control infection completely. It may have merit as a first aid dressing.

(b) The casein films devised by Curtis of Baltimore (formula — casein 30%, sodium lactate 5%, sodium sulphathiozole 3%, ethyl alcohol (95%) 25% adjusted to a pH of 8.2). This is a stiff solution which can be buttered on the wound and dries to a film in a few hours. It is water soluble. The film remains clear for ten days, is pliable, does not harm tissue cells and does give off sulphathiozole in amounts sufficient to inhibit bacterial growth.

(c) Sheets of cellulose acetate in which sulphonamides have been mixed.

(d) By far the most interesting and promising piece of work in this line is that of Schmitt of the Massachusetts Institute of Technology. He has succeeded in isolating pure collagen from beef tendon and rats' tails and from this makes sheets of various types, thick and thin, smooth or sticky, tanned or plain, tanned on one side and sticky on the other (duplex sheets). Sulphonamides may be incorporated in them and they can be sterilized. When moistened the sheets become adhesive like glue and can be fastened to the body. To exclude plasma loss he suggests the use of bentonite, a clay of such fine particles that the interstices between the cells are plugged with it and the plasma leak is prevented. Preliminary trials seem to indicate that benotine paste with sulphonamide really diminishes plasma leak from skin. This work is of great value for another reason. The manufactured collagen can be spun into threads of synthetic catgut.

(e) There are several other types of film of less interest. Hogg sprays the burn with latex which then forms a thin film of rubber, adherent to normal skin but not to burn. It is water-proof and can be used to enclose sulphonamide powder (probably dangerous). Captain Kelly has produced interesting combinations of tannic acid and gelatin; a gummy substance which can be spun into fabric or rolled into sheet. Value is uncertain.

None of the films so far devised have had extensive trial and none seem as good as tannic acid. Nonetheless their development should be encouraged. It may well result in the development of a new type of pellicle which will seal wounds from infection and provide bacteriostasis. There is, however, growing evidence that the use of sulphonamides on the surface of extensive burns is dangerous. An undetermined and sometimes great amount may be absorbed. Also in the presence of necrotic tissue their action is uncertain.

5. Methods of Burn Treatment Based on New Principles, Chiefly the Vaseline Pressure Dressing of Koch

Two surgical experiences have led independently to the idea that burns might well be treated with occlusive dressings, i.e., Trueta's experience with war compound fractures and Koch's experience with wounds of the hand.

Surgeons who have used Trueta's method of treating compound fractures not

unnaturally have been prone to treat burns in a similar fashion. The argument is: a burn is a serious wound not unlike a compound fracture. It should respond to debridement, vaseline dressing and an occlusive plaster. There are isolated reports of the merits of this treatment.

Koch's work on injuries of the hand led him to appreciate the value of cleansing the wound, a bland application to the surface and pressure dressings to prevent oedema. He has translated this experience to the treatment of burns and with some remarkable results.

His principle is so to clean the burn as to convert it from a contaminated wound to a clean wound, then to cover it with sterile vaseline and over this place a bulky dressing held on with an elastic bandage. This is to prevent oedema and plasma exudate. If he achieves adequate cleansing of the wound, infection is eliminated and the occlusive dressing prevents contamination. His treatment stresses unduly the local treatment of the burn and minimizes the importance of shock, disregards completely the problem of toxaemia and can only accept infection if it occurs under the dressing. Yet his results are remarkably good and many surgeons think he has advanced a new method of treating burns which is superior to the tannic acid method. The principle of adequate cleansing is sound. (It is done under anaesthesia and with copious washings with soap and water followed by sterile saline). The vaseline provides a bland dressing. The pressure dressing really *does* prevent oedema and exudate of plasma if applied properly. He manages to get it on every part of the body.

Koch's(15) method and his results are impressive. It would be of greater value if some bacteriostatic or antiseptic could be added to the vaseline. If the burn is of full thickness infection is common and then is poorly handled by Koch with dressings of Dakin's solution *once every second day*. An extended trial of this method is justified.

There have been many modifications and variations of the general principles of the vaseline pressure dressing method chiefly in the material which is applied to the burn after debridement and before the pressure dressing is applied. There is considerable agreement in the principle that under certain circumstances such pressure dressings can prevent swelling of the part and plasma loss. Some experiments of Drinker are impressive. A dog's paw if encased in plaster after scalding shows no swelling, has very little increased lymph flow and less toxaemia. There may be great practical difficulties in the use of this method and considerable skill may be necessary to use it properly, but the principle of pressure to control plasma exudate seems valuable and important. Some related plans of treatment are:

—The Montreal General Hospital plan. Debridement, sulphonamide emulsion and pressure dressing left undisturbed for two weeks, then early skin-grafting.

—Owens of New Orleans uses debridement, saline dressings, cellophane covering, pressure dressing and early skin-grafting.

—Cope of Massachusetts General Hospital dispenses with debridement as needless. This is based on Colebrook's work demonstrating the bacteriostatic power of the skin probably present in the sweat. Without any cleansing the burn is dressed with borated vaseline strips and covered with a pressure dressing. An important part of Cope's work has been the demonstration that the blister fluid of burns contains sulphonamides in a concentration comparable to the level in the blood. Hence early administration of sulphonamides (intravenously if necessary) en-

sures the formation of blister fluid containing a high concentration of sulphonamides.

6. The Management of Shock

In this summary of new work being done on burns, the emphasis has been on the local treatment of the burn. It is true that the largest amount of new work is in that field but there is general acceptance of the importance of the problem of shock and general agreement on the manner of its treatment. The question of toxaemia is ignored except for Drinker's research. More work should be done on the question of burn toxaemia.

7. The Management of Infection

In the attempts to control the infection in the burn area, the emphasis is on the sulphonamides. The proven merits of such antiseptics as Dakin's solution for the moment are overshadowed by the newer chemotherapy of the sulphonamides. We are greatly in need of a good antiseptic. Colebrook's experience at Glasgow with penicillin may indicate that this substance be more widely used. Champ Lyons' report upon its use in Boston would indicate that it has great merits in the control of infection. At the moment infection in a deep burn is the least easily controlled problem.

8. Catastrophies Caused by Fire

Studies of the fire catastrophes which occurred at Boston on November 28, 1942, where five hundred people died(16), and at St. Johns, Newfoundland on December 12, 1942 where ninety-nine people died(17), indicate that when fire breaks out in a crowded building, death occurs from many causes other than the actual burn. The chief causes of death are respiratory lesions; suffocation, carbon monoxide poisoning, poisoning by irritant fumes which produce an effect like phosgene. The number of burns to be treated after such a catastrophe is comparatively small. Those who escape are little burned. There are many more cases of respiratory poisoning than burns. The management of the large number of seriously injured and dying patients which pour into a hospital after such a catastrophe presents special problems which can only be successfully solved by a properly functioning organization designed to deal with catastrophes. Every first-class hospital should develop such an organization to handle smoothly the large numbers of patients who would pour into the emergency department after such a catastrophe. The dead must be separated from the living. The victims must be examined to determine the extent and nature of their injuries. Supplies of plasma and the equipment to administer it must be available. Treatment of shock and the actual burn should be standardized and simplified. For this reason Cope's plan of borated vaseline dressing without preliminary cleansing has much to recommend it. It certainly permits the efficient management of a large number of burns in a short time.

Conclusions

Under the stimulus of war needs investigation into problems related to burns is being energetically pursued. New forms of treatment are being introduced, some of undoubted value. The pathology of burns is being clarified. Standardized and simplified treatment suitable for the management of large numbers of casualties is outlined. Though much is still obscure in the problem of burns, at least one good result of the war has been the increase in our knowledge of how best to treat burns.

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PHOTOGRAPHS

196 BLOOR STREET WEST

THE CHEMISTRY OF MUSCULAR CONTRACTION

JOHN FIRSTBROOK, 4T5

When considering the evidence for the various views on the chemistry of muscular contraction, it is important to have a clear idea of the experimental procedures involved and to differentiate between the use of cell-free tissue extracts, muscle brei, intact isolated muscle, and muscle possessing its normal blood supply.

In discussing the chemical changes occuring in contraction of muscle, we might consider in turn lactate formation, phosphorous metabolism, oxygen consumption, and so on. But, it is possible to gain a clearer idea of the present position if we give some historical account of the concepts which have led to it.

History

That a muscle contracting anaerobically produces lactic acid and carbon dioxide, has been known for many years; in fact, lactic acid was first isolated from muscle by Berzelius in 1807. Because of the production of carbon dioxide, it was believed that the chemical changes in contraction must be oxidative, and Hermann postulated a giant molecule, "inogen," contained in muscle, which served as an oxygen store. Fletcher and Gowland Hopkins, in 1907, showed that there is very little lactic acid in resting muscle, but, that mechanical injury, heat, chloroform, or anaerobic stimulation increases the amount proportionately to glycogen loss. They also demonstrated that the carbon dioxide which appeared in anaerobic contraction had been liberated by lactic acid from the bicarbonate in the muscle fluids. They showed that lactic acid was oxidized to carbon dioxide and water after contraction was over, and they believed that it was completely oxidized.

In 1913, Hill found that the heat of muscular contraction was the same per unit of tension developed aerobically or anaerobically. He considered this evidence that chemical contraction changes were non-oxidative even in the presence of oxygen. But, it can be shown by thermodynamic considerations that the relation of tension developed to heat produced is independent of chemical changes and depends only on the mechanical system of the muscle. Hill was interpreting the Pasteur Effect to mean that fermentation is inhibited by *the process of Respiration.* Because he thought that the anaerobic (fermentative) processes were unaffected by the presence of oxygen, he believed that aerobic processes (respiration) did not take place during muscular contraction. Pasteur (1876), however, conceived of fermentation being inhibited by *the presence of oxygen gas.* If, then, the Pasteur Reaction is valid, contraction can not involve solely anaerobic chemical changes in the presence of a free supply of oxygen throughout the muscle; and recent work supports this concept.

Hill had shown that the heat liberated aerobically after contraction could account for the oxidation of only part of the lactic acid produced; and he thought, therefore, that the rest was resynthesized to glycogen. Meyerhof, in 1920, extended Hill's theory, showing that oxygen oxidizes only 1/5 of the lactic acid which disappears, providing the energy, he believed, for the resynthesis of the remaining 4/5 to glycogen. In support of the Hill-Meyerhof theory, Hill and Hartree, in 1923, were able to draw up a thermal balance sheet accounting for all the heat

liberated by active muscle in terms of the Meyerhof cycle. Embden (1926) showed that some lactic acid was formed after tetanus, indicating that glycogen breakdown was not the primary source of contraction energy. But Meyerhof and Lohmann promptly declared this to be an artefact due to over-stimulation, and Hill, two years later, found no heat production anaerobically after a series of twitches, concluding that no lactic acid formation takes place after contraction is over. It was not until 1931 that Meyerhof and Schulz found that post-contraction lactic acid production was not an artefact.

With the discovery of phosphocreatine in muscle by Fiske and Subbarow and by the Eggletons, in 1927, there began a new chapter in the study of muscle chemistry. It was found that phosphocreatine was hydrolysed during contraction and resynthesized in oxidative recovery; Nachmansohn showing, the following year, that anaerobic recovery up to 30% may take place. Davenport and Sacks (1929) demonstrated that glycogen could react with phosphocreatine to form hexosemonophosphate, which Emden and Zimmerman, two years previously, had postulated as an intermediary in lactic acid formation. Fiske and Subbarow made the suggestion that the products of phosphocreatine hydrolysis served to buffer lactic acid by virtue of the fact that phosphoric acid was a weaker acid than phosphocreatine. As we shall see, this suggestion has been revived by Sacks, but, at that time, it was obscured by Lundsgaard's hypothesis.

Lundsgaard discovered in 1930 that frog muscle in which lactic acid production is blocked by iodoacetate, contracts until all the phosphocreatine is broken down, and then passes into rigour. Most of the phosphocreatine reacts with glycogen to form hexosemonophosphate, while hydrolysis of phosphocreatine, the chief change in normal contraction, takes place to a smaller extent. The phosphocreatine breakdown is proportional to the energy liberated, and Lundsgaard believed that here was the immediate source of contraction energy. In 1931, Meyerhof, Lundsgaard and Blaschko reported that the heat of hydrolysis of phosphocreatine was sufficient to provide the energy for contraction, and early the following year, Hill, reviewing the "Revolution in Muscle Physiology," outlined a scheme whereby phosphocreatine breakdown provided the energy of contraction and all lactate formation was concerned with phosphocreatine resynthesis.

Several objections to the Lundsgaard hypothesis were immediately obvious. Nachmansohn, as mentioned, had found that only 30% of the phosphocreatine was resynthesized anaerobically in spite of large lactic acid formation; Lehnartz (1931) had observed that lactic acid formation continued for 5 minutes after tetanus, whereas the resynthesis of phosphocreatine which did take place was complete in 1 minute; and Cattell and Hartree (1932) showed that delayed anaerobic heat formation lasted longer than 5 minutes.

Using muscle extract at pH 8 to 9, Meyerhof and Lohmann (1932) added adenylpyrophosphate and obtained a production of phosphocreatine and adenylic acid. They concluded that adenylpyrophosphate provides the energy for phosphocreatine resynthesis and is itself resynthesized by the formation of lactic acid. But, Lohmann (1934) using muscle extract at pH 7, found that adenylic acid would combine with phosphocreatine to form adenylpyrophosphate and creatine. He therefore drew up a scheme of the chemical changes occuring in muscular contraction as follows: (1) The initial

energy-producing reaction is adenylpyrophosphate breakdown. (2) Recovery begins when phosphocreatine resynthesizes adenylpyrophosphate. (3) Later, phosphocreatine is resynthesized by energy released from lactic acid formation. (4) The final recovery is by oxidative reactions—the Meyerhof cycle oxidation of lactic acid and resynthesis of glycogen.

Abandoning the use of isolated muscle and muscle extracts, Sacks and Sacks, in 1933, using a technique developed by Davenport for freezing in situ mammalian muscle with intact blood supply, found that during the first few seconds of contraction there was no hydrolysis of phosphocreatine but that lactic acid and hexosemonophosphate were formed, the latter deriving its phosphate from phosphocreatine. On longer stimulation, phosphocreatine hydrolysis begins while the rate of accumulation of lactic acid and hexosemonophosphate decreases. Prolonged stimulation leads to a decrease in hexosemonophosphate and in lactic acid concentration and to a resynthesis of phosphocreatine. According to the Lundsgaard hypothesis, phosphocreatine breakdown would be expected first, with lactic acid formation later, while the accumulation of anaerobic metabolites would be expected to increase. Sacks and Sacks therefore concluded: (1) The energy-liberating reactions are normally oxidative and are anaerobic only in anoxia or relative anoxia. (2) The primary anaerobic reaction is formation of lactic acid from glycogen, supplemented by formation of hexosemonophosphate from glycogen and phosphocreatine. (3) The primary function of phosphocreatine is to supply base for lactic acid neutralization.

Oxidation in Muscle

As evidence for the oxidative nature of contraction, Sacks and Sacks found that accumulation of anaerobic metabolites ceased sooner in rat muscle than in rabbit muscle which is known to have a poorer blood supply and, therefore, poorer oxygen supply. Improved methods for measuring the time-course of oxygen consumption have been reported in recent years. Urban and Peugnet (1938) have studied the reduction of cytochrome c spectrographically. Using frog gastrocnemius, they showed that reduction of cytochrome c and the yellow enzyme begin at the same time, which suggests that contraction energy comes from immediate oxidation. Millikan (1938), using myohaemoglobin as an indicator of oxygen tension, has shown that in cat's soleus there is an increased oxygen consumption within 1/5 second (the minimum time lag of his method), and maximum oxygen consumption within 1 second, after the start of contraction. He concludes that either, (a) contraction is a direct oxidative process or, (b) there is a very fast anaerobic recovery. Oxidative recovery rates of phosphocreatine, adenylpyrophosphate, and of glycogen have been shown by Sacks to be slow to account for the steady state (wherein the supply of oxygen is sufficient to prevent the accumulation of anaerobic metabolites). Flock, Ingle, and Bollman (1939) from studies on contracting rat muscle in situ, conclude that contraction is fundamentally oxidative and that lactic acid production is due to an initial phase of oxygen deficiency.

The Fuel of Muscular Exercise

Although glycogen has been considered as the main fuel of muscular activity, Flock and Bollman (1940) find that its resynthesis is very slow and conclude that it is definitely limited as a source of energy in continued contraction. Gemmill suggests that glycogen initiates activity while glucose carries on. Glucose

in the tissue fluid bathing the muscle cell may pass into the cell by phosphorylation and it has been found that during contraction, as oxygen is taken up, the glucose in the tissue fluid decreases. The observation of Krebs that iodoacetate poisoned muscle can not utilize glucose has been shown by Shaw to be due to excessive iodoacetate. Just sufficient iodoacetate to inhibit glycolysis does not depress utilization of glucose in muscle nor of added glucose. There is evidence that ketone bodies and lactic acid may be utilized by contracting muscle.

The Mechanism of Anaerobic Contraction

The chemical changes occuring in anaerobic contraction are: (1) decrease in glycogen and increase in lactic acid; (2) decrease in phosphocreatine; (3) increase in inorganic phosphate and hexosemonophosphate.

There are two schools of thought with regard to the mechanisms involved in the above changes. One school believes that reactions which occur in cell-free muscle extracts containing the muscle enzymes are identical with those occuring in intact muscle. Cori, Embden, Meyerof, Needham, Parnas, and Warburg have contributed to our knowledge of glycolytic schemes involving creatinephosphate, and adenylpyrophosphate. The other school believes that phosphocreatine hydrolysis and hexosemonophosphate formation are independent of lactic acid production in intact muscle. Sacks (1940), using radioactive phosphorous, showed that neither phosphocreatine nor adenylpyrophosphate acts as a phosphorous transporter in glycolytic activity during contraction. He considers the formation of hexosemonophosphate as a mechanism for conservation of glycogen, for hexosemonophosphate does not diffuse as does lactic acid. Hexosemonophosphate is not an intermediary in formation of lactic acid in the intact muscle cell, although in extract, where the cell membrane is lacking, it may be.

The Role of Phosphocreatine

Sacks offers the following evidence for the theory that phosphocreatine breakdown contributes toward the buffering capacity of the muscles. (a) Rabbits fed acid-forming foods show increased hydrolysis of phosphocreatine during muscular activity. (b) Phosphocreatine resynthesis is 12 times too slow to be considered as dependent upon lactic acid formation. (c) The resynthesis of phosphocreatine is associated with lactate removal by diffusion into the blood stream, rather than with lactic acid formation.

Among the many questions remaining to be answered about the chemistry of muscular contraction are the role of the respiratory enzymes and the nature of the oxidative reactions which liberate the energy for aerobic contraction. Until very recently, the answer to the most baffling problem of all, what Millikan calls the "Yawning Chasm" between the metabolic processes and the structural changes associated with muscular activity, has been completely obscure. In 1939, Englehardt and Ljubimova, working in Moscow, in attempting to obtain pure preparations of the enzyme adenylpyrophosphatase which catalyzes the dephosphorylation of adenylpyrophosphate to adenosinediphosphate, found that they could not separate the enzyme from the muscle protein myosin. It has been shown that adenylpyrophosphate has a direct effect on the optical anisometry of and increases the extensibility of myosin threads. This is the first demonstration of the relation between the mechanics and the chemistry of muscle.

Englehardt suggests that adenylpyrophosphate is concerned in the relaxation of the muscle fibre, a process which he likens to the charging of an electrical condenser preparatory to the discharge of energy. References to this work are given by Millikan and Englehardt.

The writer is indebted to Dr. A. M. Wynne for criticism and advice.

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TRACER ISOTOPES AND RADIO-THERAPY

N. B. KEEVIL, M.Sc., PH.D.*

OUTLINE

Physical background 179
Sorting of atoms 180
The cyclotron 181
Detection of radioactivity 182
Dynamic equilibrium in the living body 182
Physiological studies with tracers 183
Pathological studies with radioactive tracers 185
Possible aid in diagnosis 186
Radio-therapy 187
Internal radiation therapy 187
Selective slow neutron therapy 188
Fast neutron therapy 188
Radium therapy 189
Radioactive tracers in nutritional research 189
The part of the physicist 190

PHYSICAL BACKGROUND

Most elements consist of mixtures of atoms with different masses but the same chemical properties. Throughout natural processes, the proportion of heavier and lighter atoms in any one element remains remarkably constant. During the last decade, however, ways have been found of separating isotopes of many of the lighter elements, such as carbon, hydrogen, oxygen and nitrogen, thus producing samples chemically identical with the normal elements, but marked by their differences in nuclear mass.

While isotopic separations are not yet practical for the heavier elements, nature has tagged the heaviest of these in a different way. Their nuclei are metastable, and break down into lighter or more stable elements at definite rates of decay.[1] Particles are expelled from their nuclei in a succession of atomic disintegrations, until finally a stable element is formed. These processes liberate huge quantities of energy compared to ordinary chemical reactions, which makes it possible to detect extremely minute quantities of radioactive elements.

Since 1934 other elements, including those of intermediate weight, have been made radioactive by artificial means. Atomic projectiles such as hydrogen nuclei are fired at a target of normal atoms. Occasionally an atomic nucleus is penetrated and becomes radioactive and unstable. In passing to stable form, it usually emits a high-speed electron which disrupts the outer structures of atoms and molecules in its path through surrounding matter, and is readily detectable with sensitive counting instruments.

The machine most commonly used for making radioactive elements artificially is the cyclotron, which has proved capable of producing beams of deuterons of 17 million electron volts energy, which in turn can produce intense beams of neutrons,[2] now being used in radiation

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[1]Only one naturally radioactive element, potassium, is a common constituent of the human body, and this is one with an extremely slow rate of disintegration emitting weak radiation.

[2]A *neutron* is a neutral particle with approximately the mass of a *proton* (the nucleus of a normal hydrogen atom); a *deuteron* is the positively charged nucleus of heavy hydrogen (deuterium) and consists of a proton and a neutron. An *electron-volt* is the energy acquired by an electron falling through a potential difference of 1 volt and is equal to 1.589×10^{-12} ergs (MEV=million electron volts). The nucleus of every element except helium has been found to react with neutrons to produce other elements. *Fast neutrons* produced by radioactive sources or from cyclotrons, are slowed down by hydrogenous material (12 collisions with hydrogen nuclei reducing the energy from 5 MEV to 0.0001 MEV); *slow neutrons* thus produced are more efficient in some nuclear reactions.

therapy of cancer as well as in the transmutation of matter (Figure 1).

Sorting of Atoms. Before reviewing the results of applications to medicine, a general survey of some of the tools of the applied nuclear physicist will be made.

During the past three years complete facilities for detecting "labelled atoms" have been installed at the University of Toronto. By "labelled" or "tagged" the element in the chemical combination which is to be followed in the experiment. If the sample is identified by the presence of a heavier isotope as a tracer, such as an excess of heavy nitrogen (N^{15}) relative to normal nitrogen (N^{14}) in an amino acid, the course of the nitrogen-containing group is best followed by sampling a fraction of a gram of tissue at desired intervals, liberating the nitrogen, and

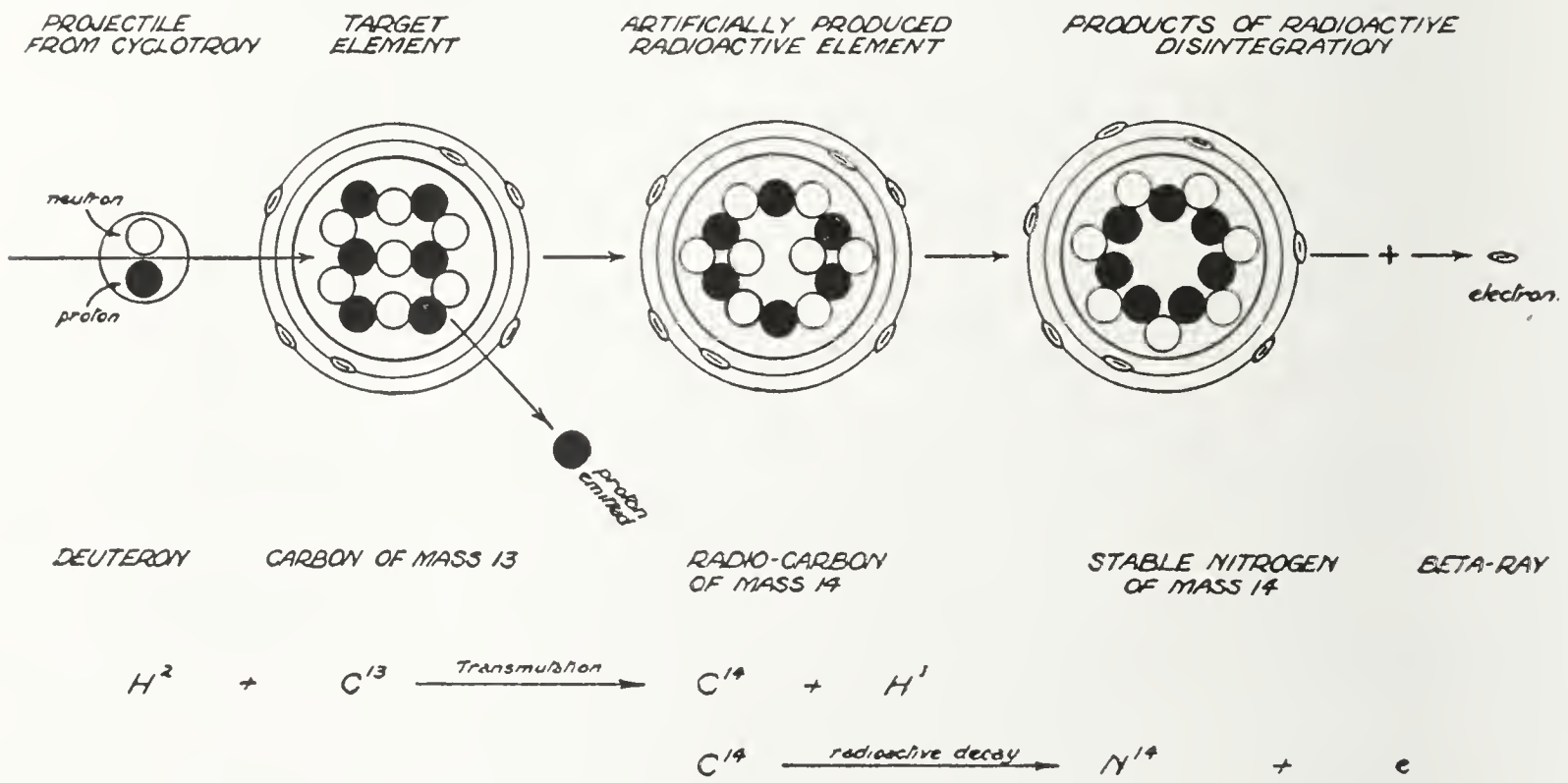

FIGURE 1.—Schematic representation of the production and decay of a tracer element (not to relative scale, the size of the nucleus with respect to the atom as a whole being comparable to the size of the sun relative to the solar system). Note that when radio-carbon of mass 14 emits an electron the nucleus is left with an additional unit of positive charge, and one external electron is acquired to produce a stable uncharged nitrogen atom. One half of C^{14} atoms in a sample decay in 1000 years. Radio-carbon of mass 11 can be produced more easily than C^{14} by bombarding boron (B^{10}) with deuterons; the half-life of this product is only 21 minutes.

atoms is meant atoms distinguished from others of their kind by unique nuclear differences but with the same chemical properties.[3] These can be used as *tracers* to follow the course of particular elements or groups in biological processes.

A "tracer" for use in biophysical studies may be prepared by introducing to a sample radioactive or heavier isotopes of determining the excess of N^{15} over N^{14} by means of a *mass spectrometer* (Fig. 2).

The fundamental principles of the mass spectrometer are actually quite simple, and it may be well, because of certain similarities, to examine its operation before outlining the action of the cyclotron. The essential part of the instrument shown in the photograph (Fig. 2) lies between the two circular pole faces in the center of the magnet. Gas or vapor of the substance to be analysed is introduced at one end of a semicircular tube 10 inches

[3]Actually the heavy isotopes of the lightest element, hydrogen, differ considerably in their *rates* of reaction, but not in their *types* of reactions.

in diameter at a pressure of 10^{-4} mm. of Hg. Here, a beam of electrons from a tungsten filament ionizes the gas. Positive ions so formed are drawn towards a metal plate by an electrical field, and those passing through a slit in this plate are further accelerated by fields, V, up to 1200 volts. These ribbon-like beams of ions, after leaving the electrical field, are bent in circular paths by a constant magnetic field. Since the radius of curvature of any such beam depends upon the mass of the constituent particles, the ionic masses passing through an exit slit at the other end of the semi-circular tube are determined by the initial accelerating voltage, V. Thus it is possible, by adjusting V, to *sort atoms according to mass,* and to determine quantitatively, from the currents which the ion-beams produce, the relative abundance of isotopes.

The Cyclotron. If an ion-beam such as that discussed above were further accelerated, on leaving the exit slit, by the same potential difference, V, the velocity of the ions would be doubled, and their radius of curvature in the magnetic field increased. If at the completion of a circular path they passed again through the field, V, their velocity would be again doubled and they would move in an even greater circle. This is what happens in the cyclotron; the ions are accelerated at each half-circle of their path by an electrical field applied in the proper direction.

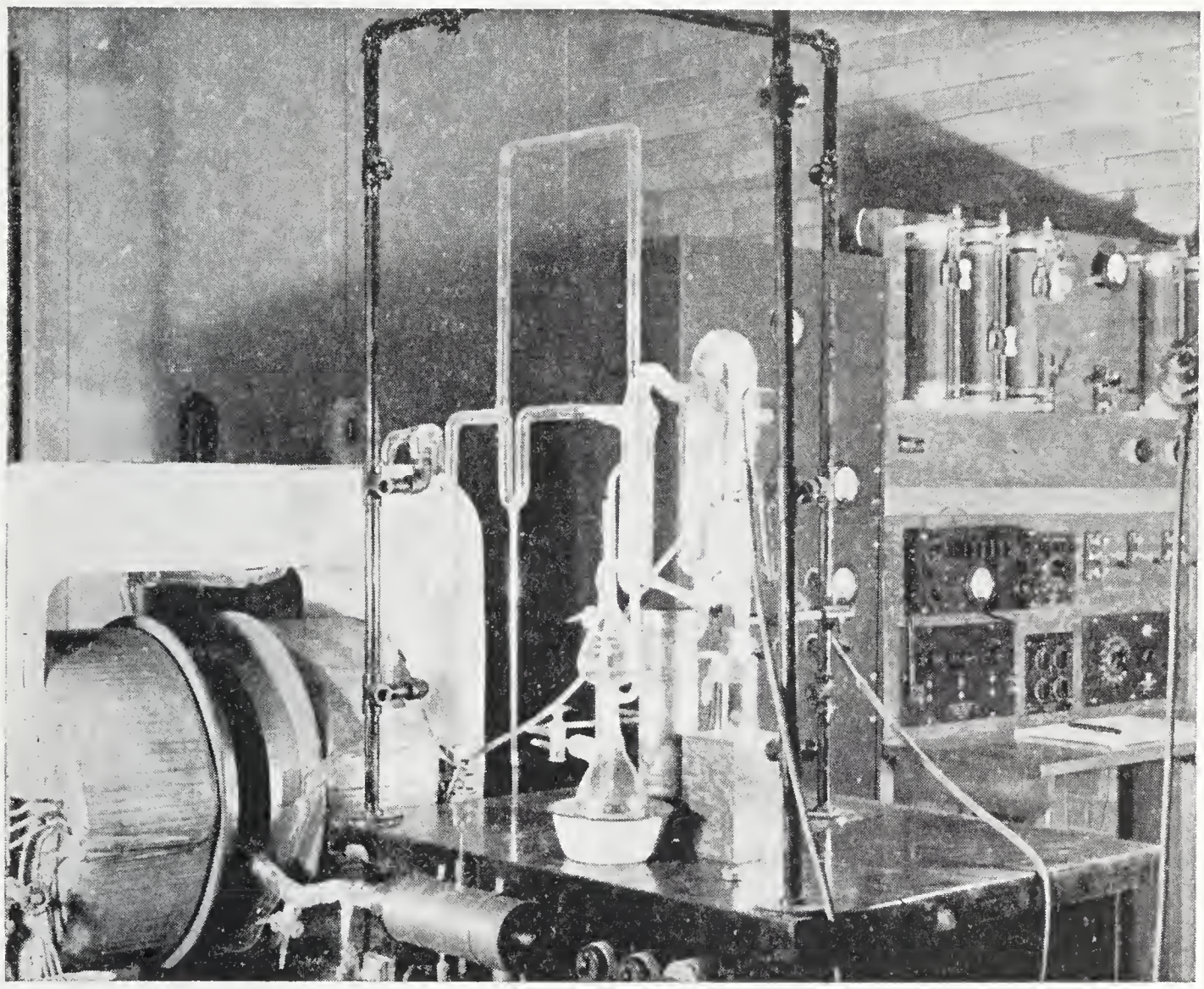

FIGURE 2.—Mass Spectrometer. At the left of the photograph is shown the magnet housing the tube which sorts voltage-accelerated positive ions according to mass by their different paths in the magnetic field. Beside the magnet is shown a part of the glass high-vacuum system, and on the right, some of the electrical controls.

The particles spiral outward because, as they gain speed, they have more centrifugal force. Practically, what makes the cyclotron possible is the fact that the time for any one kind of ion to complete the semi-circular path is independent of velocity. Therefore, an alternating current field synchronized with this time can be applied to the two hollow D-shaped electrodes of the cyclotron. The ions spiral within each dee, being accelerated at each half-circle by the voltage across the gap between them. By the time a beam of deuterons spirals to the outer edge of the dees it has acquired tremendous energy due to the high velocities of the ions. The beam is controlled by electrical fields and absorbers so as to hit the desired target. If it hits beryllium, radioactive boron and fast neutrons are produced for further atomic bombardment or for neutron-therapy; if it hits carbon of mass 13, radioactive carbon is produced (Fig. 1).

Detection of Radioactivity. Modern radioactive counting instruments are of two general types. In one, the rays pass into an ionization chamber, where the ions which they produce are separated by an electrical field applied between the walls and a central electrode. The momentary current produced by ions streaming towards the electrodes may be measured by a suitable current-measuring device which, if sensitive enough, can pick up current pulses from individual alpha-ray ionization.

The other type involves a Geiger-Muller tube with smaller radius and greater potential field applied between an outer cylinder and a central coaxial electrode. Ions formed near the latter by radioactive rays are given enough energy by the high electric field to produce finally an avalanche of ions, which cause a much greater momentary change per particle than does the ionization chamber method. Both methods and their various modifications have their own particular advantages.

The importance of having suitable and highly sensitive counting devices is that greater dilutions in the body are allowable in radioactive tracer studies, or conversely, smaller quantities of the valuable tagged atoms need be used in experimentation.

Dynamic Equilibria in the Living Body

A striking result of the use of tagged atoms in physiological research has been a new picture of extremely rapid assimilation and replacement of essential elements and molecular groupings in the living body. To illustrate the speed of assimilation, the popular lecturer may dose himself with tagged sodium contained in dilute salt solution, then demonstrate by means of a Geiger counter and loud speaker its passage from his stomach to his hands in two minutes. Tagged iodine similarly travels to the tissues within a few minutes, and quickly concentrates in the thyroid.

More fundamental experiments, using radioactive phosphorus or heavy isotopes of carbon, nitrogen, or hydrogen to tag organic compounds, have shown that while the concentrations and structures of these compounds in the body remain constant, there is a continuous rapid turnover of the component elements and groups of even such large molecules as fats and proteins. For example, interconversion of fatty acids, hydrogenation and dehydrogenation, elongation and equivalent shortening of the carbon chain, occur continuously, and fat molecules

themselves are being formed and broken down all the time.[4]

Heavy nitrogen and, more recently, radioactive sulphur have been used to tag amino acids for protein investigations, disclosing similar dynamic equilibria in the nitrogen chemistry of the living body. Peptide linkages open and close, the alpha-amino groups of liberated acids migrate to nitrogen-free compounds, and carbon chains change to those of other amino acids. This interaction extends even to the specific antibodies of the serum of immunized animals.

Phospholopids are rapidly formed from inorganic phosphates administered orally or intravenously, the rates varying for different organs and tissues. All show exchange and replacement of phosphorus, the rate being highest in liver, kidneys and small intestines, lowest in muscle and brain. As expected, the rate of turnover was higher in newborn than in adult animals.

It is largely the results of experiments with tracers that have led to the conception that many chemical reactions constitute metabolic cycles, which continuously refresh and replenish all the cells of the living body and maintain a normal balance throughout widely varying stimuli by automatic adjustment of these rapid equilibria. Tracer isotopes have been able to follow such processes without themselves disturbing them, in a complex system so balanced that the total amounts and structures of its individual units remain unchanged. They have a promising future in the study of intermediary metabolism, the rate and extent of molecular turnover under various conditions.

[4]The essential food constituents, linoleic and linolenic acids, are not involved in these automatic processes; similarly the amino acid, lysine, does not take part in dynamic protein equilibria.

Physiological Studies with Tracers

Nitrogen excreted by the animal has been found by tracer studies not to be derived directly from food, but rather to represent a *sample of the mixture* resulting from the extensive and continuous reaction of organ proteins whose equilibria are disturbed by the introduction of dietary amino acids. The iron balance was previously supposed to be adjusted by rate of elimination; now, however, rate of absorption from the digestive tract appears to be the important factor, while iron in feces may be caused by blood destruction.

Experiments in which about ½ gram of tagged iron was fed to dogs showed absorption of 12.7 per cent iron administered to animals rendered anaemic by bleeding, and less than 0.24 per cent for normal dogs. Animals with iron-deficient tissues absorbed five times as much as those with blood deficiency, but most of the new iron was found in the muscle and blood. Ingested iron was found to be mobilized in the red blood cells within a few hours, too soon to be accounted for by the formation and release of new erythrocytes. More recent experiments with human subjects fed labelled ferric ammonium citrate have indicated that iron absorption in the human body is also regulated by the reserve iron stores in the tissues.

The thyroid gland is chemically a most remarkable organ because of its ability to concentrate iodine received from the blood by a factor of ten thousand. Tracer atoms have shown that this process begins immediately after iodine enters the blood, although there is a preliminary diffusion to various tissues, particularly lung, kidney, liver, spleen, heart, bile, and submaxillary gland. Quantitative data have been obtained on absorption rates and amounts

in the normal thyroid, as well as on the rates of formation of di-iodo-tyrosine and thyroxine. An interesting technique, autoradiography, has been developed to study distribution of radioactive elements in various tissues. A section of the tissue placed on an X-ray film will cause darkening of the film in proportion to the concentration of radioactive elements. Such radioautographs of thyroid tissue show that the accumulated iodine is fairly evenly distributed, with slight difference in amounts in cells and colloid. This was not true of abnormal thyroid tissue.

Element 85, a radioactive element very recently discovered, is the member of next higher weight than iodine in the halogen series of the periodic table. Its relationship to iodine was demonstrated by similarity of uptake by the thyroid and elimination by the body.

Labelled phosphorus has been shown to concentrate in the bone marrow (near the joints, as autoradiographs show) and in the following other tissues, in decreasing percentages of fresh weight: liver, stomach and small intestine, heart, kidneys, lungs, blood, muscle, skin, and brain. The maximum concentration of radiophosphorus in mice is reached in about ten hours, except in the brain, which absorbs and releases phosphorus much more slowly, indicating a more gradual turnover of phospholipids here. Radiophosphorus has been used to test theories of anaerobic muscular contraction. In cats, the relative radioactivity of phosphocreatine phosphorus was only one-tenth that of inorganic P in resting muscles, while relative activities of P from adenosine triphosphate and hexosemonophosphate were still less. This differential distribution was retained in stimulated muscle, showing that phosphorus in these compounds was not involved in formation of lactic acid as postulated by the Embden-Meyerhof schema.

Migration of phosphorus between cells has been shown to be of chemical or enzymatic nature, but that of sodium and potassium proceeds by selective diffusion. Radio-sodium administered to dogs as the chloride distributed itself uniformly throughout the extra-cellular water within 100 minutes. Erythrocytes exchange some sodium slowly with the plasma, the process being one-half complete in 12 hours; otherwise, no appreciable amounts enter the intracellular phase. On the other hand, there is a forty per cent exchange of radio-potassium and intracellular K in 100 minutes in dogs, though this exchange is relatively slow in rats, rabbits, and humans. It is obvious that the behaviour of these cations cannot be explained by the classic theory of the semi-permeable membrane. Experiments with radio-chlorine (in vitro at 38°C.) have demonstrated that equilibrium is established between chloride of cells and that of serum in less than an hour.

Manganese has been found to be poorly retained by the rat on a normal diet, 90 per cent being excreted, mostly by the intestines; of that absorbed, the largest amounts were found in liver, bone, and muscle.

Pentavalent (radio-) arsenate injected in subtoxic amounts into the ear veins of rabbits was widely distributed, concentration in the liver, lung, muscle, bone, and tumor reaching a peak at three hours and continuing until the twelfth hour, by which time 50 per cent of the administered arsenic had been eliminated in the urine. Surprisingly little is taken up by the brain.

Highly radioactive copper must be used for tracer studies if toxic results are to be avoided. Using such a product pre-

pared by proton bombardment of nickel, studies were made of anaemic copper-deficient and iron-deficient rats. The former retained more copper, the highest concentrations being in the kidneys and liver. A small fraction was found in the bone marrow, and increased enzyme activity associated with hematopoietic activity of the bone marrow was observed 24 hours after feeding copper to deficient rats.

Only small traces of radio-calcium were present in the soft tissues after intravenous or oral administration, most of it being selectively stored by the bone. Strontium, chemically similar, is taken up by the bones to a lesser degree and excreted more rapidly but, like calcium and unlike phosphorus, is not taken up appreciably by the soft tissues. Because of this property and its non-toxicity, as well as its ease of preparation and suitable radio-active characteristics, radio-strontium is useful for specific irradiation of the bones. Feeding of radio-calcium and strontium to pregnant mice has disclosed considerable migration (5 to 25 per cent) of these elements to the foetus during the last days of pregnancy and early lactation. Since the specific activity of the bones of the newborn mouse is higher than that of the mother's, the last phosphorus to be formed in the bone appears to have been the first to leave.

There are few reports of work done with other elements than those mentioned above, but isotopes can be made of most elements in the periodic table and the possibilities for research are almost unlimited. Among the elements to be studied zinc seems promising because its role is so little understood. Its remarkable concentration in plant seeds, its natural occurrence with insulin, and the effects of dietary deficiency in zinc which indicate that its absence may inhibit riboflavin absorption and utilization are suitable matters for further study.

Pathological Studies with Radioactive Tracers

Tracer techniques have been particularly useful in a number of pathological studies. For example, it was not thought likely that phosphorus had a part in production of fatty livers, since the phospholipid content remains constant from the normal to the fatty state and back. Only by labelling these molecules was it shown that the rate of phospholipid turnover is an important factor, it being accelerated by substances which prevent or cure fatty livers in rats, retarded by cholesterol, which accentuates their production.

Malignant cells contain abnormal amounts of phospholipids, with a rapid turnover comparable with that in the liver. The nuclei of malignant cells take up more phosphorus than those of normal cells, but similar absorption by rapidly growing normal live cells suggests that the rate is influenced by the rate of cell multiplication. Calculations show that 3×10^4 molecules of complex tetranucleotide are synthesized per second in the lymphoma nucleus.

In human leukemia, as well as that of mice, radio-phosphorus was selectively accumulated in the leukocytes rather than in erythrocytes or plasma, and localization in the bones and bone marrow has been observed at autopsy.

Studies of bone tumors have shown that radio-phosphorus is localized on the metastases, and that radio-strontium is deposited more rapidly by tumor cells than by surrounding uninvolved bone. The latter discovery proposes a possible method of selective radiation therapy.

Radio-iodine has been of great use in studies of pathological conditions of the thyroid. Results have not always con-

firmed existing views. The chief advantage of the radioactive method is that experiments can be performed *in situ* without any abnormal treatment of the subject. By means of readings recorded automatically from a counter tube placed under the patient's chin, quantitative determinations of iodine in tumors have been made over a period of five days to four weeks after giving radio-iodine orally as the sodium salt. In normal individuals, the maximum iodine uptake by the thyroid was reached in 1 to 2 days, after which its concentration fell off very gradually. In non-toxic goiter the uptake curves were similar in shape but up to twice as much iodine was taken up, indicating that the thyroid functioned normally but took up more iodine because of its larger size. In toxic goiter, the initial absorption was 3 to 4 times the normal amount, but the accumulated iodine was more rapidly lost. In hypothyroidism, the iodine uptake was as low as one-tenth normal. Comparison under the microscope of radioautographs of normal and diseased thyroids with corresponding tissue sections showed fairly even distribution of iodine between the cells and colloid of normal tissue, some concentration in the cells and acini of non-toxic goiter, and accumulation of iodine in the colloid of cells which had undergone hyperplasia, apparently associated with increased ability of these cells to concentrate administered iodine from the blood stream. This appears to be a compensatory process of uninvaded thyroid cells, regardless of the cause of the hyperplasia. Cancerous cells, in the instance studied, had lost their ability to concentrate iodine.

It has already been pointed out that iron uptake is now understood to be controlled by absorption from the small intestine, rather than by controlled excretion. Studies on anemic dogs and humans have shown that much larger amounts are absorbed when circulating and tissue iron are depleted by repeated bleedings and iron-poor diet. However, the iron absorption is less than normal in diseases such as pernicious anemia in which iron stores are known to be abundant. Nor does the anemia accompanying chronic infections usually cause increased uptake of iron. On the other hand, pregnant women who are not noticeably anemic absorb as much as ten times the normal amount of iron. The mechanism by which abundance of iron reserves can control amount of gastro-intestinal absorption is not understood. It has been concluded that the plasma is the initial site of absorption, since iron is concentrated too rapidly in the red blood cells to have been involved in their new formation and release. It would be interesting to transfer blood containing labelled iron from a normal individual to an anemic subject and to follow its subsequent history.

Few other tracer atoms have been used to date in pathologic studies. Of these we may mention manganese, whose absorption has been studied in normal chicks and those suffering from perosis. Absorption of phosphorus and sodium from the intestinal tract of insects is being studied as a preliminary to investigations of insect pathology appropriately concentrating on the action of poisons used for their extermination.

Possible Aid in Diagnosis

Before considering the use of radioactive isotopes for therapeutic irradiation of specific tissues, it is felt that their possible value as an aid to diagnosis should be pointed out and kept in mind. While such applications are at present more idealistic than practical, a comparable accumulation of observations may put

them on equal footing with some clinical methods. In particular, the quantitative data now available for the accumulation of radio-iodine in the thyroid fall on curves so different for various types of thyroid deficiency that their study might be able to compete with metabolism tests in diagnosis of the condition of this gland. Also there are wide differences in percentages of iron absorbed in certain types of anemia which, on further study, may prove a definite aid to diagnosis.

Radio-Therapy

Internal Radiation Therapy—The biological action of radioactive emanations has provided the clinician with a new weapon for treatment of neoplastic disease. Tracer research has pointed out the way to selective internal radiation therapy by showing localization of phosphorus in the pathologic tissues of leukemia and similar diseases, and of strontium in bone tumors. Radioactive strontium has been used in the latter case because of its similarity to active calcium, whose weaker radioactivity makes it unsuitable for therapeutic use. It has been found that the dosage of this substance must be very delicately adjusted, since it concentrates also in normal bone and an overdose will suppress hematopoiesis. It will probably be most useful in conjunction with external radiation.

Radio-phosphorus also is limited in use by the fact that it is taken up by bone to a greater extent even than by tumor tissue, and should therefore be most valuable for treating diseases which involve the bone marrow. Several hundred patients with chronic lymphatic leukemia were treated with radio-phosporus at the University of California, with results considered promising. The proper amount of dosage is still a subject for research and varies with the individual, but small frequent doses have been generally used, in order to extend the radiation over the periods of highest sensitivity of various cells to increase utilization and decrease undesirable retention by the body, and to avoid depression of erythropoietic activities where there is already a tendency in this direction. Some biologically active radiation remains in the body for 25 days or more after the final dose. This fact must be considered in planning the course of treatment, and careful watch must be taken for each individual of total leukocyte count, number and type of pathological cells, and hemoglobin level. A definite drop in the number of reticulocytes or platelets often precedes a drop in red cell level. In spite of these pitfalls, it is believed on theoretical grounds that when methods of treatment have been worked out more fully, internal radio-therapy will prove more valuable than external radiation. To date, a number of lives have apparently been prolonged by this method of treatment, but several more years must elapse before evaluation can be made of the relative efficacy of internal and external radiation therapy.

Radio-phosphorous treatment has apparently been of great value in chronic myelogenous leukemia, polycythemia vera, and lymphosarcoma. In fact, workers at Memorial Hospital, N.Y., have been able to say, on the basis of their treatment of 22 unselected cases of lymphosarcoma, "It is believed that P^{32} should be used either primarily or secondarily in virtually all cases of lymphosarcoma." These workers did not find damage to the hemopoietic system which could not be fairly ascribed to other causes. The work with Hodgkin's disease has not proceeded far enough for evaluation. Results with multiple myeloma, metastatic carcinoma, and some other conditions are not encouraging, but further research on these

diseases is justified because of their ordinarily fatal outcome.

The use of radio-iodine in treatment of hyperthyroidism is still in the test stage. As already shown, the degree of hyperplasia corresponds to the degree of iodine retention. A few patients have been treated and have responded favorably, with one relapse requiring a second course of treatment. It has been found that carcinomata do not concentrate radio-iodine, but its storage has been reported in a metastasis from a thyroid carcinoma.

The prerequisite of internal radiation therapy is knowledge of the selective localization of an element or substance which has desireable radioactive properties. The advantages over X-ray are ease of application and absence of radiation sickness. Expense and limited availability are disadvantages, at present.

Selective Slow-Neutron Therapy—Another way of obtaining localized irradiation is by means of boron or lithium. These elements may be administered to the body in some desirable form and the subject exposed to slow neutrons. The boron and lithium capture these neutrons and emit energetic alpha-rays in their own vicinity, producing an intense local effect, whereas slow neutrons themselves exert a feeble effect. The difficulty is in fixing the boron and lithium at the desired locations. An ingenious method used is to incorporate lithium in a dye, the sodium analogue of which is known to be preferentially absorbed by tumor tissue. Much remains to be done in this promising field.

Fast-Neutron Therapy — Intense collimated beams of neutrons from large cyclotrons have been used in the treatment of cancer, and much is expected of the method because of the relatively dense ionization which neutrons produce as contrasted with X-ray beams now in use. With the technique developed to date, one or two roentgens of diffuse total-body radiation have been unavoidably received in the time required to give 100 neutron units, but this does not appear to affect the blood. The general irradiation may, however, contribute to the roentgen sickness almost always observed.

Fast neutrons penetrate the skin to about the same extent as 300 kv. X-rays. Skin reactions appear in considerably shorter time than those produced by X-rays, though the degrees of reaction are comparable. About 110 n (neutron units) and 675 r (X-ray, or roentgen units) is the threshold erythma dose.

Several forms of cancer were treated by exposures of 600 to 1000 n over a period of about three weeks, or until the skin reactions became severe. In general, the methods of treatment were similar to those employed in X-ray therapy. Systemic reactions were produced in certain cases, such as a severe diarrhea after irradiation of the upper abdomen and mucositis in patients treated about the head and neck, so severe as to cause great difficulty in eating. General reactions were anorexia, followed by nausea and general malaise in less than half the cases, and in a few cases by vomiting and dehydration during treatment or the month following treatment.

The results of treatment of patients with presumably incurable cancer were encouraging, 50 per cent being alive at the end of the twenty months' period. About 48 per cent of the patients showed partial regression and 17 per cent complete regression of the tumor. Several autopsies showed that death was caused by ulceration or by cancer in regions not treated, while the cancers treated by neutron therapy had disappeared in these cases. In general, primary tumors did not respond so well as metastases.

At present, research is progressing on the best means of applying neutron therapy. It is fairly obvious that different procedures will have to be worked out for neutrons because their mode of ionization is so different; X-rays produce their effect by removal of secondary electrons whose ion-tracks are narrow, but the tracks of alpha-particles and recoil nuclei produced by neutrons are wide and filled with thousands of times as many ions. Whether the wide tracks exert greater biological effects is yet uncertain. The fundamental effect produced by both X-rays and neutrons is destruction, and the difference may be of degree rather than of kind. It would be well to know more of the secondary processes following this primary destruction, but it is more important to be sure that normal tissue will recover favorably while the tumor tissue is destroyed. In this respect the dense local destruction produced by fast neutrons seems to promise more success than X-rays. Recent studies have shown neutrons to have more effect, proportionately, than X-rays on tumor cells in the resting stage.

Radium Therapy—Radium has never been given so thorough a test in cancer therapy as it might have had if more radium had been available. Its chief uses have been in interstitial, intracavitary, and superficial applications, and in conjunction with other methods of treatment. With the supervoltage X-ray machine as much radiation can be produced as would be obtained from all the refined radium in the world. Still it must be remembered that the radiations are not strictly the same, and that radium implanted directly in a tumor has certain obvious advantages over X-ray irradiation.

Other forms of radiation therapy are in various stages of development. Supervoltage X-ray generators are now installed; the Sloan high-frequency resonance transformer produces 1½ MV. X-rays, and compact Van der Graaf electrostatic generators can produce X-rays in excess of a million volts. These high voltage machines could also be used to produce 1.5 MV. cathode rays, which give a particularly favorable distribution near the surface, penetrating to a depth of only 8 mm. of living tissue. Beams of electrons of 2.3 MEV and 20 MEV have also been obtained by the newly developed Betatron.

Radioactive Tracers in Nutritional Research

The outstanding advantage of radioactive tracers in research is that the amounts of tracers can usually be so regulated that equilibria of the body are not appreciably affected, and the radiations produce no pathological reaction.

It should be possible to study the destination and behavior of a food constituent in normal subjects without the necessity of destroying nutritional balance, and from a series of experiments to determine the normal level in the body, and thus establish the body's needs. The relative digestibiltiy of various foodstuffs may also be determined; where complex problems of synthesis arise, materials might be produced *in vivo*.

Studies have already been commenced on the metabolism of proteins, fats and carbohydrates, as well as on vitamins.

Vitamin B_1, labelled with radio-sulphur during synthesis, was administered intramuscularly to normal and deficient human subjects. In both cases rapid interaction with that already in the tissues was indicated, and rapid destruction of thiamine was shown by the appearance of amounts of inorganic sulphur in the urine up to 15 per cent after a short time. Even after 36 days without vitamin B_1, the

injection of 8 mg. of radio-B_1 over a period of 3 days resulted in the elimination of 0.8 mg. of pre-existing thiamin. Destruction of the vitamin was again shown after returning to a B_1-free diet. Normally about 10 per cent is destroyed in the human body every 24 hours.

The Part of the Physicist

The potentialities of radioactive tracers in medical work are obvious, and one can think of many problems which promise to be straightforward and productive, but a word of caution is necessary. In the first place, practical knowledge of the field is not readily acquired, and in the second place we in Canada are seriously limited by lack of radioactive materials, no cyclotron being available for their production.

But the problems do not end with the possession of a cyclotron, or a convenient source of materials. Radioactive isotopes of most of the elements have been prepared during the last few years, but these vary widely in ease of preparation, in rate of decay and in energy of radiation. One cannot, therefore, think of a problem and decide to use radioactive nitrogen, without enquiring as to whether a suitable radioactive isotope of nitrogen is available, whether another isotope may not be more suitably employed, whether the molecules in question can be synthesized, and so forth (Table I).

Considerable chemical work is required in purifying material from the target after bombardment with atomic projectiles, in synthesizing suitable compounds for biologic use, and in preparing material for measurement at the end of the experiment. Choice of a suitable compound for the tagged atoms is important. One would not use certain elements, for example, in ionized form, have deuterium in a labile position, or attempt to place labelled carbon in a benzene ring.

In ordinary experiments 1 tagged atom in 10^{12} to 10^{15} is used, and it is assumed that these have no unusual biological effect. It is important in some investigations to be sure that the radioactive dose is below the threshold for physiological effects, and this point must be determined. From metabolic studies of mice it has been found that 36 microcuries of phosphorus can be safely used in tracing phospholipid reactions in the brain, 16 in blood metabolism, 8 in the liver, and still less for studies of the chromsomes because of their well known sensitivities to radiations. Such limits in concentration obviously determine the degree of dilution detectable in the experiment.

TABLE I

Isotopes Most Commonly Used in Biophysics

Prepared by Thermal Diffusion	*Prepared by Chemical Methods*	*Prepared by slow Neutron bombardment*	*Prepared by Deuteron bombardment*
Carbon	Deuterium	Bromine	Sodium
	Nitrogen	Iodine	Potassium
		Silver	Sulphur
		Gold	Chlorine
			Phosphorus
			Manganese
			Iron
			Copper
			Arsenic

Choice of animal must also be considered. The expense and rarity of tagged atoms have limited the work in many laboratories to small animals such as mice and rats. Dilution in the human body is about 1 to 10,000, which is not serious if one has a cyclotron to produce the material.

Often the time factor is important, and this may be governed by the rate of physiological or pathological processes, the rate of decay of the radioactive isotope, partly by the tolerable dilution, and by the strength of the initial material and sensitivity of the counting instrument.

The physicist can be of much help in regulating the production and use of material, in protection of the workers from radiations, for improving counting techniques, in calculations of results and errors, and assisting in the physical aspects of intrepretation.

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SILICOSIS AND TUBERCULOSIS AS RELATED TO THE MINING INDUSTRY

S. C. ROBINSON, '44

Silicosis as a disease entity or complicated by tuberculosis forms an industrial hazard of major importance. The growth of Canada's mining industry has made it a medical and engineering problem which has commanded the attention of leading workers of both professions. This article will attempt to describe some of the findings arising out of these investigations, and to explain how these have been applied in preventing and controlling the diseases. Many of these methods of control have been seen in the Geraldton gold mining area.

Historical Note

It has long been known that certain pneumoconioses are associated with a high tuberculosis mortality; in fact a phthisis-producing industry was usually first recognized through it association with a high tuberculosis mortality in middle life. In 1915 E. L. Collis reported that he had shown by statistical analysis that this high tuberculosis mortality was associated with the dust of free silica (1). Later it was demonstrated that this silica need not be in the pure form in order to produce silicosis and to be associated with the high tuberculosis mortality. More recently a number of fatal cases of silicosis uncomplicated by tuberculosis have been reported from South Africa, and at least one in this country.

Silicosis—the Disease

1. *Etiology*

The essential factor in the causation of silicosis is silicious dust. Most of this material is not uncombined silica, but consists of minerals in which silica is in combination with other elements to form silicates. It is generally accepted that it is the very finest components of the dusts which are concerned with silicosis. Various figures have been given, but it can be stated with reasonable assurance that particles less than 5μ in diameter are dangerous. Larger particles are removed from the respiratory passages by ciliary action. The smaller particles can gain entrance to the alveoli and in experimental animals it has been observed that these particles also cause changes in the passages. The bronchial epithelium shows scattered areas of flattening and loss of cilia. Presumably this prevents further dust particles from beling eliminated. These fine particles have a relatively great area and therefore a high rate of solution. Thus fibrosis results.

Under the impact of drilling, blasting, and other mining operations, particles down to less than 1μ in diameter are produced in immense numbers. Such minute particles are probably kept almost indefinitely in suspension by convection currents and by Brownian movement.

2. *Contributory Factors*

(a) *Gas.* In blasting operations carried out underground, considerable quantities of nitrous and carbon monoxide fumes are produced. In animals exposed to toxic gases alone for periods of more than two weeks, widespread changes of the bronchial epithelium characterized by degeneration, desquamation and absence of cilia are seen. Occasionally large numbers of monocytes are present

in the alveoli (2). The effect on the human respiratory apparatus is probably similar.

(b) *Infection.* This is probably of major importance only in conditions where tuberculosis is associated with early silicosis.

3. Manifestations—Pathological and Clinical

From evidence accumulated in South Africa (where silicosis has been extensively studied) it appears that the disease may take one of three forms:—

(a) *Silicosis of the Simple Type* (uncomplicated by secondary infection).

Evidence: (i) There is no microscopic evidence of the presence of an infective factor. (ii) Guinea-pigs innoculated with material from these lesions failed to develop any tuberculous changes. (iii) The degree of silicotic change in these cases as determined at post-mortem examination is proportional to the amount of silicious residue extracted from the lungs. (iv) This type of lesion can be produced experimentally with no accompanying tuberculous infection.

Pathology: There is a nodular fibrosis' miliary in type, in the lung substance and under the pleura. Dust has been transported to these foci by monocytes which remove the particles from the alveolar spaces. These cells undergo a change in which they become fixed lustrocytes. Permanent structural and functional damage to the lung results. The lymph glands at the root of the lung are early affected and there is always some accompanying bronchitis and sometimes emphysema.

Clinical Manifestations: Progressive shortness of breath is the cardinal symptom and chronic emphysema usually results. The X-ray appearance in established cases corresponds closely to the pathological changes and gives the distinctive appearance of a clean-cut miliary nodulation of varying degree. The disease is characteristically progressive. In a few instances (reported from South Africa), where the concentration of dust in the atmosphere breathed has been very high, a rapidly developing and fatal type of silicosis has been produced—aptly called acute silicosis. The total duration in these cases was 9-17 months. These are in marked contrast to cases in Northern Ontario mines which generally require 17 to 18 years' previous exposure to underground conditions to develop.

(b) *Silicosis of the Infective Type*

Etiology: It is universally accepted that the effective occupation of the lungs by silicious dust not only leads to a fibrosis, but creates an increased predisposition to the development of tuberculosis either at sites where latent tuberculosis already exists or at sites where silicotic lesions are developing or have developed and at which bacilli may arrive and become arrested. Also it would seem reasonable to suppose that the damp undergound conditions favour droplet infection and therefore any open case is exceedingly dangerous to other men who will inevitably be working with him in the confined space.

Pathology: The lesions, if in a nodular form, are irregular in size and outline, but may be larger and often extensive areas of massive fibrosis or fibroid consolidation, lacking the distinctive characteristics of either unmodified silicosis or tuberculosis. It has been noted in many cases at this stage that the disease is characterized by a self-limiting fibroid reaction. Innoculation of guine-pigs

with material of such lesions produces a tuberculosis in the majority of cases (3).

Clinical Manifestations: The customary physical signs of active tuberculosis are absent, and toxic symptoms and deterioration of general health are either absent or unimportant. In other respects symptomatology resembles simple silicosis except that stage for stage the amount of disability is greater. The X-ray appearance is in keeping with the pathological changes described.

Duration: Infective silicosis may be present from the first or it may appear as an intermediate stage, often of long duration, between simple silicosis and active tuberculosis and silicosis. It has been suggested that the limiting fibrosis often seen here is due to the additional stimulus to fibrosis supplied by the silicotic element.

(c) *Tuberculosis with Silicosis*

Etiology: In what respects this differs from the infective type of silicosis is not clear, but it would be reasonable to presume that the size of the infective dose and the patient's individual resistance play their parts here.

Pathology: The picture is that of active tuberculosis, modified by whatever silicotic lesions are present in the area examined. In terminal stages the spread of the infection to other organs is not uncommon.

Clinical Manifestations: The condition is the conjugation of silicosis with a clinically detectable, active and physically deteriorating tuberculosis. This condition of active tuberculosis may supervene at any stage in the course of silicosis, but often appears only as a terminal complication. The customary local and constitutional signs of respiratory tuberculosis are present. These are usually followed by a rapid break-down in general health, although more chronic cases are seen. That the three clinical and radiographic types of the disease described conform to the general pathological conception quoted above was evidenced in the post-mortem findings in over 1000 deceased miners in South Africa.

Methods of Control

(a) *The Dust Itself*

It is known that all dusts are not equally harmful, but satisfactory qualitative analysis of mine air is more or less ineffectual at present, due to: (1) some selective settling of the constituents taking place before the dust passes through the filter; (2) some of the particles (less than 1μ in diameter) not being trapped by the filter, or being attached to larger fragments or being coagulated by greasy matter usually present in the mine air; (3) the presence of many particles in the samples examined which are too large to permit of entry into the alveoli; (4) the fact that the composition and texture of the dusts vary in different mines and for different mining operations. Samples from ore bin dust may not be truly representative of underground dust.

Thus the only recourse is to eliminate any and all dust, regardless of composition. Nearly 90 per cent of the mass of mine dust in hardrock mining is composed of particles less than 6μ in diameter, with the greatest concentration (by weight) at or just below 2μ. By far the greatest number of particles are less than 1μ in diameter.

(b) *Dust Counting*

An instrument called the konimeter is used to obtain samples for dust counts. 5 cc. of the mine air is drawn into a chamber and projected through a fine

orifice on to a ground glass screen to which a suitable adhesive has been applied. The screen may be rotated so that 15 different samples may be taken on the single screen. The screen is removed and treated by heat and acid to remove all organic material, carbon particles, etc. A special microscopic attachment permits counts to be made of particles less than 5μ in size. In the Geraldton area, counts of more than 300 per cc. of mine air are considered to be unsatisfactory, i.e. prolonged exposure entails the risk of developing silicosis. When adequate precautions are not taken in mining operations the count at the end of an 8-hour shift rises to many times 300 per cc. Unfortunately, the rise is most marked in drifts, stopes, etc., where the men are actually at work and where ventilation is of necessity not optimal.

(c) *Dust Control*

The principles of control will be outlined briefly. Obviously dust control is the most effective prophylactic measure against silicosis.

(1) *Ventilation:* This is often very difficult, but since dust and irritant gases can be removed by adequate ventilation, mines should go to no little expense to design and install efficient ventilating systems. Often special air passages must be drilled and kept open under winter conditions, fans must be installed and many engineering problems must be solved.

(2) *Drilling:* Water must be used to combat dust in these operations. Modern drilling machines cannot be operated without a stream of water being forced through the hollow drill steel to the face. Thus dust is washed down before it can escape into the air.

(3) *Cleaning Drill Holes:* The holes must be cleaned of rock particles before explosive can be introduced. This should be done with a mixture of air and water, after the dust and gravel have been moistened thoroughly. The wet particles settle more rapidly than the dry, due to their greater weight.

(4) *Blasting:* This should all be done at one time so that miners need not re-enter and work even for a short time in the atmosphere of dust, smoke and gas which exists. After the blast the dust count reaches many thousand per cc. Improved mining techniques make this possible in most cases.

(5) *Preparation for Work:* Air must be blown for four hours if possible to remove smoke, dust and fumes. If an air-water mixture is used, the rate of dust settling is increased.

All loose rock, the walls, equipment, etc., should be all washed down with water before each shift begins its work.

Compressed air should not be used for cleaning cars, floors, etc., as much dust is thus raised.

Where these precautions can all be put into effective operation, the miner can work in a relatively gas- and dust-free atmosphere.

(d) *Aluminum Dust:* Extensive expermental work with aluminum dust has been done by Dr. D. A. Irwin and others of the Department of Medical Research of this University; Dr. W. D. Robson, Chief Surgeon to the McIntyre mine; and J. J. Denny, M.Sc. (4).

Only a brief summary of their findings can be given here.

1. Small quantities of metallic aluminum greatly decreases the rate of solution of silicious material in the beaker.

2. The development of silicotic lesions can be practically eliminated in experimental animals dusted for various

periods with silicious material by the addition to the atmosphere of 1 per cent of metallic aluminum dust.

3. The aluminum dust particles should be 5 less than μ in diameter and grease free.

4. The aluminum reduces the toxicity of the dust chiefly by coating the particles with an insoluble and impermeable coating, but also by flocculation, and adsorbing silica from solution.

5. Aluminum dust inhaled in large quantities over long periods of time "showed no effect on the general health of the animals and no evidence of toxicity or damage to tissues" (4).

It has been noted in air-craft factories, where workers who buff the metallic surfaces inhale large quantities of aluminum dust, that there are no toxic effects due to this dust.

6. In animals where the aluminum dust has been administered for a half-hour period following the regular dust exposure, no silicosis has resulted.

These results suggest many applications to the mining industry for use in situations where the mine dust cannot be otherwise controlled. The placing of aluminum dust in the mine air presents exceedingly difficult engineering problems and in most mines it has not been considered feasible. The inhalation by miners of aluminum dust for a brief period after they finish work—possibly while they are waiting at the shaft to be brought to the surface—is a technique which would seem to bear investigation. Of course the widespread use of aluminum for these purposes is not possible during the war, so diligent application of the other methods of preventing the disease must be exercised.

(e) *Tuberculosis Control:* Due to the peculiar susceptibility of early silicotics to tuberculosis it is most important that not only the miner but also his family should be tuberculin tested at least every 6 months and chest plates should be taken where indicated. In one Ontario mining community (the Geraldton area) over 95 per cent of the population have voluntarily submitted to this examination, conducted with the view to removing dangerous cases from contact with the miners.

(f) *Examination of Miners:* Miners in most areas are filmed twice annually and before employment. Needless to say, all diagnosed or suspicious cases of silicosis or tuberculosis are forbidden to work underground.

In conclusion, it appears obvious that from the point of view of compensation, and more importantly because of the incapacity suffered by those who develop silicosis with or without tuberculosis, the application of these principles of control throughout the mining industry must be strictly enforced.

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THE EDUCATION OF THE FEEBLE-MINDED

HOWARD C. HAZELL, B.A., '44

In order that the present educational system, with respect to the feeble-minded, may be fully appreciated, it is valuable to look back, in perspective, at the evolutionary steps by means of which this new outlook has been attained. There is a close parallel between this change and the one that normal education has undergone. Until a few years ago, it was thought that the mind was sort of an empty barrel into which the apples of education, in terms of the three R's, could be stored. Education was looked on as a process of storing up unlimited numbers of facts that could be culled at will from the storehouse as necessity demanded. However it was found that many of the "apples" disappeared. With the advent of a psychological approach to education, the entire concept changed from looking on education as a means whereby the mind could be stored with facts, to the realization that the important thing to develop in children is a wholesome personality with its accompanying habits and activities, in order that a satisfactory adjustment to psychologically traumatic experiences and to all the demands of the environment could be made. In the light of this new concept the entire educational set-up for normal children has been revised. Similarly it was formerly assumed by educationists and psychologists, that feeble-minded children differed in kind rather than degree (1). They were considered to be a separate species. Consequently, in educating them, systems were devised on this basis. For example, consider "Seguin's Physiological Method" (1), which was the first system formed for the education of feeble-minded children. He believed that the mind could be divided into special entities, each being strengthened by special exercise, and that the system of education for the feeble-minded should be different than that for normal children. Binet, the French psychologist, held the same view in his early life. He, along with others, changed his viewpoint when Experimental Psychology discovered that the differences between feeble-minded children and normal children were of degree and not kind. This fact is well substantiated. Statistics show that the feeble-minded form the lower end of the curve of distribution and that the frequency of any type of feeble-mindedness decreases as the lower end of the curve is reached or as the degree of defect becomes greater. In England for each one thousand of urban population there are 0.3 per cent idiots, 1.2 per cent imbeciles and 5.2 per cent morons. Good diagnosticians have difficulty in putting the feeble-minded in one class or another. As a result, the entire concept of education for the feeble-minded has changed, and is being put into practical use because it means that absolutely different methods of teaching are not necessary for the mentally deficient but that they can learn just like ordinary children up to the level of their mental age.

In examining the educational system, the question as to whether they are equally feeble in all abilities gives a lead as to what type of education will be most profitable for them. Feeble-minded children may equal normal children with respect to physical development and sensory capacity. They are inferior to normal children in motor control and the intelligence necessary to direct such control. They are especially deficient in intellectual growth;

abstract thought being almost an impossibility. These observations have an important bearing on pedagogy because it is seen that this type of personality can grapple with things rather than ideas. Therefore the feeble-minded will profit best from education that will lead to skill in eye-hand co-ordination and in tasks where physical and sensory capacity is essential. In view of these facts, it may be said that education with respect to feeble-minded children is that directed learning, mostly of an external nature, which has for its aim the development of habits that will enable such a person to live at that maximum of efficiency of which he is capable in his environment with respect to the social, moral, occupational and economic spheres.

There are two situations in which such an educational aim can be carried out. One of these is the institution. It is by no means the ideal. Davis says: "Children, whether normal or subnormal, must have the chance to receive the educational and social value of the home and school and for this reason the institutionalization of such children should be avoided" (3). However, there are some situations in which it cannot be avoided. Subnormal children can be conveniently classed on an I.Q. basis. Those having an I.Q. beween 0-20 are known as idiots, between 20-40 imbeciles, and between 40-70 morons. The morons may be subdivided into low, middle, and high grade. Children who have an I.Q. between 70-90 are known as dull and retarded children. The feeble-minded of the idiot and low grade imbecile type are of necessity cases for the institution. Feeble-minded people who are a menace to their community, and could not profit by special school training, cases of bed patients and those adult cases whose presence would naturally be obnoxious in a special school for boys and girls are fit cases for the institution. The other situation in which the feeble-minded may be educated is the special school. It can handle all those people of the high imbecile, moron, and dull and retarded types, giving these children as well as special school training the obvious advantage of a normal life in a community. Therefore to obtain a true knowledge of the educational programme for the feeble-minded, both the institution and the special school must be considered. Consider first the institution.

The Ontario Hospital at Orillia is typical of institutional life (2). A number of experiments were devised to study their educational problems with regard to their patients. One of the first problems met was that of enuresis. It is obvious that training in such a fundamental habit is a prerequisite to any other type of training. In order to see if patients having enuresis problems could be trained, twelve typical cases were chosen. The two qualifications necessary for elegibility on the experimental team were the ability to walk and to have a definite enuresis problem. The ideal in view was to establish control on rising, before and after meals, and on going to bed. The method used to study the problem was a psychological one since medical examination showed no physical impairment. Each child was put on a definite routine consisting of a trip to the toilet at definite time intervals, which were lengthened as the number of days increased, on the basis of a perfect record for any time interval. This process continued until the child was able to assume responsibility. All of the patients showed improvement over a three months period, which proves that the feeble-minded can be trained in fundamental habits if sufficient time and care be taken with such training. The method used in such training must be a routine method, which will

produce definite fixed habits with respect to the thing being trained and also establish a co-ordination in one sphere that may be carried over to another. The children were also put on a routine for other fundamental habits such as eating, sleeping, washing and dressing, in all of which improvement was shown. Therefore in subnormal children response is given to systematic training, and the starting point for such training is in the fundamental habits.

Another area of investigation was that of play. The same group was used in this experiment as in the fundamental habit experiment. The playground was situated outdoors in a bright, sunny location. It was equipped with a slide, swing, see-saw, sand pile, a cupboard of utensils, two wagons and three kiddy cars. The children were placed in this playground for one hour, during which time they were closely watched. There was no direction given to their play, the purpose of this being to see what the children would do spontaneously, the results of which could be used in determining that directed play from which they would be most likely to profit. It was observed that the games they liked best were those of manipulation and locomotion. They liked to throw things about. An expression of rhythm was found in most of the children. They showed a real deficiency in group play interest. A great extreme in forms of behaviour was noticed but there was a noticeable lack of quarreling. These observations were used to give organized play to the children for the purpose of training them in the traits in which they were most obviously deficient, especially those of socialization. Such simple exercises as joining hands to form a circle or marching to music in a circle, were performed. These simple movements provided locomotion, a chance for expression of rhythm and simple teaching in group manoeuvers. Again, at the end of three months a decided improvement was observed in social adaptation, rhythmic expression and control in arm and leg movements.

The last field of investigation in the institution was that of occupation. Three types of training were given. The first two of these was the elementary field work for juniors and adults. All the members of these two groups were composed of low grade imbeciles, ranging in I.Q. from 25-40. These two groups were to be trained to clear land. The junior group, consisting of twenty-eight boys, was taken to a training ground and for one hour a day they did various tasks. These tasks consisted of shovelling sand into a trough, carrying stones from one circle to another, piling bricks neatly, and sorting and piling rocks. These occupations are those involved in clearing land. The senior group carried out a similar training in a large field covered with stones and bricks. This group cleared twenty acres in one summer. By this training much of the idleness and resulting discontent has been stamped out of the hospital and a happier community life established.

The second type of occupational training was given to a group of seventy-five girls. Its object was to teach the girls to make mats and to learn to sew. The method was a process that started with simple rag ravelling, increasing in more difficult steps until cutting and sewing were being done and finally things being made. At the end of two months all the pupils showed decided benefit from the training, even those with exceptionally low I.Q. This training, just as with the boys, had a very decided effect on the morale of the female patients and their entire community life.

The last type of occupational training

was concerned with work on the wards. A ward work training class was organized to train those very mentally deficient patients to do tasks that higher grade patients were doing. The purpose of this was to give these patients a chance to learn something themselves and to give the brighter patients a chance to learn other tasks of which they were capable. The training on the wards consisted of bed making, sweeping, scrubbing, dusting and waxing. Here again, the patients learned to do the tasks and the desired aim was accomplished.

By the experiments conducted in these areas of education in the institution, it has been shown that the feeble-minded can be trained to use what faculties they possess to better advantage, resulting in more happiness for them and a better community life in general. Therefore the institution can do real, constructive work for those people that it receives, some of whom could even leave and support themselves. However, if the child is of the high imbecile, moron, or dull and retarded types such a child should have the advantage of the special school if it is at all possible. And it is to the special school that we now turn our attention.

The fundamental habits of feeble-minded children who go to the special school may be learned at home, so that the first type of training is to develop systematic and methodical powers of observation. With this end in view, the work is directed along the following sensory lines: touch, hearing, smell, taste, colour and forms. The method employed in the training of each of these senses is such that specific tasks are given to the child which are concerned with the particular special need. If, for example, it is the sense of touch that is being developed, the child is allowed to touch various articles, feeling their shape and learning their names, after which follows a short discussion on the use of the article and its other qualities. This training is a basic prerequisite to the other types of training. When the child has completed this pre-kindergarten work he is ready to enter the kindergarten.

Manual training is a very important type of non-academic training. It is an objective way of learning by doing and in preparing feeble-minded children for future occupations. One of the outstanding features of feeble-minded children is the lack of co-ordination in the hands and fingers. These children at first cannot even pick up objects between the first finger and thumb, and their early manual training consists of grasping exercises such as picking up pins, threading beads, and paper weaving. Easy drawing lessons, painting and making pictures are of value. These simple exercises contain elements common to occupations. Paper weaving, for example, is a good preparation for sewing. At a later stage they are taught to hammer nails to a line and to sand-paper wood. Thus in manual training there is a type of purposive activity having a bearing on real life occupations.

Physical training constitutes one of the greatest aids to the physical and mental development of these children. There is a close relationship between physical and mental units. Physical units must be functioning properly at a high efficiency to produce high mental efficiency. Therefore it becomes the aim of physical training to help to produce the highest degree of mental efficiency possible. Games play an important part in the operation of this programme. They teach social adaptability. Dances, for example, are excellent for this. Games develop and improve many of the mental qualities, such as seeing, thinking, doing and sensory perception. The rules of the games serve as

a means of self-control. Games for the feeble-minded must be very elementary. For the poorest pupils, they are as simple as kicking a ball and being taught to march. These mental qualities, developed as a result of physical training, will certainly hold the child in good stead as he attempts to adjust himself to his community.

One of the most important aims of the special school is to fit the child for life and it is at this point that occupational training plays an important part. Farming is an ideal type of training for these children but it is not very practical for city life. Carpentering, plumbing, shoe-making, painting and printing are the most feasible. The students are placed in shops to learn as apprentices, still being under the supervision of the teacher. Charts are constructed to show what type of work a particular mental age is capable of doing and thus the error made in helping the feeble-minded in choosing a career is brought to a minimum, which helps the child to solve the problem of social adaptability.

Thus far, the four most important types of educational training for the feeble-minded have been considered. The feeble-minded are least proficient in academic work. Yet if the child is to be established as a normal in a community he must have some training in the higher faculties of the mind and it is possible to give such training to mentally deficient children of the higher brackets.

The teaching of numbers is part of the academic curriculum. Adding and subtracting may be taught in terms of some interest that the children have. They are very poor in abstract thought and must have their arithmetic associated with something practical that they know. Arithmetic has its greatest utility in the teaching of how to count money, calculate bills, and learning simple tables such as inches, and gallons. Such training has practical application to life. Reading is another of the subjects in the academic curriculum. The children are taught to read papers, bills, industrial signs, street car and street signs. Cutout letters, words and phrases, when arranged to form sentences, provide one of the best methods of teaching reading. Reading ability leads to a much fuller comprehension of life. Music plays an important part in the social adaptation of the feeble-minded child. Music produces a satisfaction and happiness in him. Social adaptation may be best brought about by group singing because it requires co-operative effort and activity.

Since the feeble-minded child lives in a community, in order that he may do so intelligently, a knowledge of the structure of the community with special emphasis on civics is important. This training attempts to impart such information by giving him practice in the social setting in which he is going to have to adjust; the school, home, city and the nation, as well as a general knowledge of the laws of the community.

The final part of the educational training for the feeble-minded is moral training. It is by no means least, for, as Davis says, "It will determine whether the individual rises or falls" (3). If he fails in this, all the other training is gone to waste. One of the methods used is that known as the expository, which consists of enlightenment with regard to right and wrong, moral obligations and relations between virtue and vice. This method can be best illustrated by the telling of simple stories. The other type of training in this area is essentially that of habit formation. If fixed habits of response are formed day by day, a real, constructive step will have been taken in helping the child to be socially adaptable. However,

these methods are not sufficient in themselves. A child must not be left to stand entirely alone. He needs all the instruction and help that he can get from his parents and teachers.

It has been shown by both the institution and the special school that there are methods of training the feeble-minded and that they may be trained in such a way that they are able to take an active part as a citizen in a community. It is at this particular point when a so-called feeble-minded person has established himself, socially, economically, occupationally and morally, that the name "feeble-minded" ceases to give the child its true label, if we must label. He has now proved that he can live as a normal being in the community and thus he has the right to be classed as a normal human being. This, very simply, is the true aim of education for the feeble-minded; to train, where possible, the feeble-minded in order that they may develop those habits which will enable them to take their place in a community as socially acceptable human beings.

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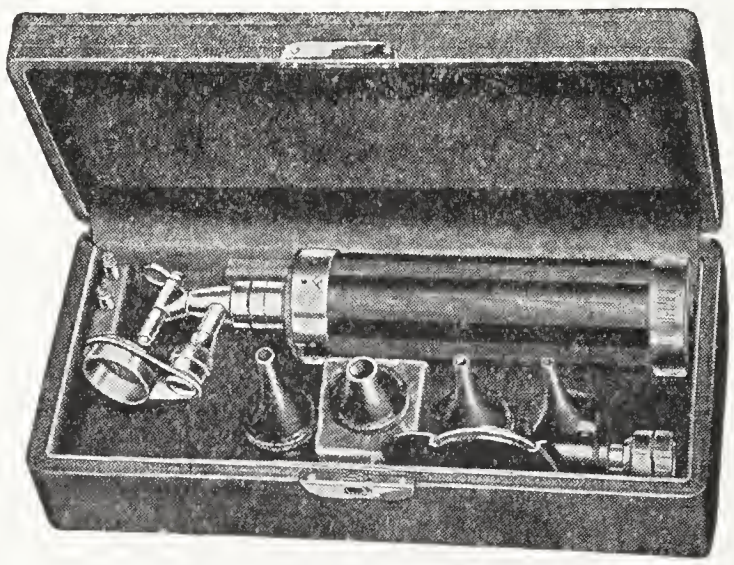

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Feature Section

F. C. JONES, Editor

YOUR OPPORTUNITY

MARY V. JOHNSTONE

Secretary, Ward "A," Toronto General Hospital

When the Feature Editor requested me to contribute to this section, many interesting observations arising from my association with the Students on Surgery, presented themselves. One of paramount importance seems worth considering.

The lay person looking on, with no vital connection other than being one of the minor cogs in the wheels, with an inquisitive and receptive mind, often perceives certain aspects of the work, of which he feels the student fails to grasp the true significance. The writer is thinking in terms of students on this particular division, but has no doubt but that it is applicable to students on any service in a teaching hospital.

On this division we have a rotation system, whereby the public ward patients as admitted, are assigned in rotation to the various students engaged on the ward. However, this ruling is elastic and can be modified without disturbing the arrangement. For example, should a student be assigned as his particular responsibility, several cases of the same nature, it is his privilege to exchange with another student. There is of course, the perennial selfish individual found in every walk in life, who appropriates all the interesting major cases, to satisfy his insatiable interest. He is rare, but he does exist and a frightful nuisance he is to his fellow students who must be up betimes to get ahead of him. I shall not attempt to solve this problem for you.

Serving in a secretarial capacity one acquaints oneself with the nature of the illness that prompts these patients to seek relief in hospital. Frequently one enquires of a student, the proposed treatment for Mrs. B. only to receive the reply—"I don't know anything about her, she is not my patient; she belongs to Jackson." If you make a similar enquiry of Jackson regarding a case not assigned to him, you invariably receive the same response.

In the teaching wards in a large industrial centre such as this, students have access to an abundance of material not found in less populated districts. The opportunity to acquire as much knowledge as can be absorbed, cannot be over-estimated. These circumstances are enhanced by teaching facilities of the highest calibre, directed by instructors with a sincere desire to impart their knowledge and the fruits of their experience, to those who will follow them, with the full realization that many of these lads will be the leaders of the future, in their chosen profession.

A group of students on this division devised a scheme, whereby each day, one of the group took the other members on rounds on all his cases acquainting them of the history, physical findings, operative findings, etc. The following day

another took it up, until they were fairly familiar with all the cases on the ward. It was a stimulating process while it lasted, but unfortunately, as many idealistic enterprises, born of enthusiasm, it petered out. This suggestion is passed on to you with the conviction that it will function if enforced.

When one tried to analyze the reason for failure of this splendid scheme, the consensus of opinion seemed to throw the responsibility on that bugbear "scut work." Consulting the Oxford dictionary one finds no reasonable definition for the term, but in the light of the ward nomenclature, it appears to indicate routine work, i.e. bloods, urines, cut downs, etc. Interested in this formidable phenomenon that could so completely overthrow the worthy project outlined, the writer decided to do a sort of Gallup poll to assess the merits of it. It was gratifying to arrive at the conclusion that generally, the students feel it is an important fundamental routine of the whole process of their career, but by no means pre-eminent. Their attitude to it was much that of a pianist or any instrumentalist to those tiresome scales and exercises one must of necessity perform endlessly with the full knowledge of their tremendous importance to the proficiency, to which an ambitious artist aspires. Let me quote from Phillips Brooke—"Routine is a terrible master, but she is a servant whom we can hardly do without. Routine as a law is deadly. Routine as a resource in the temporary exhaustion of impulse and suggestion is often our salvation."

One does not wish to dwell unduly on this subject, nor is the motive of this article to sermonize, but rather, in some small measure to convey to you that the Golden Years are not in the past or future, but with you.

There are many avenues of opportunity open to you. One of the most illuminating of these, is your privilege to attend weekly Grand Rounds; to listen in on discussions when all ideas are pooled, and even express your opinion from the store of knowledge you possess.

There are numerous occasions other than the scheduled clinics when you may contact the Clinician. Of these perhaps Sunday morning is more ideal than week days. On this day the Staff men frequently make rounds. They appreciate the interest shown by the students present.

The Nurse in charge of the ward is another appoach. She must of necessity, make rounds many times daily to listen to complaints of the patients and comfort them. You will find her co-operative and eager to assist you in every way possible. Arrange to accompany her as often as your time will permit. The extra time expended will produce satisfactory results.

EDITOR'S NOTE.—*Miss Johnstone has recently introduced into her office on Ward A a library of hundreds of reprints. These consist of articles, all carefully selected by the surgical staff and arranged by index under subjects.*

Much time and thought has gone into the preparation of this library and it is freely available to any student interested. Whether for special references, for the preparation of papers, or for further reading, senior students are urged to make use of this wealth of material.

Furthermore, the idea is an excellent one, and worthy of repetition in every ward or hospital. The scheme might even be enlargd so that students themselves could share in the selection and adding of articles to the collection.

Abstracts

RUPERT WARREN, Editor

Contributors E. T. French
H. B. Stewart
C. M. Wells

Some Aspects of the Nature of the Chemical Changes Occurring in Atheromatosis

Irvine H. Page
Annals of Internal Medicine *14*, 1741 (1941)

This represents a review of the underlying problems in the study of atherosclerosis and consequently presents a large number of not thoroughly correlated facts. *Aetiology.* Virchow first developed the view that atheroma developed as a result of strain on the vessel wall. Aschoff added the second contingency that sufficient lipid must be present to form the plaques and that this was of a cholesterol character. This contention was supported by the fact that Germans in the last war and following it showed a lower than normal incidence of atheroma due to the low fat content of their diet. The effects of the following were discussed.

1. *Level of Lipid in the blood related to the diet.*

Blood lipids are raised by high fat diets particularly in animals accustomed to low fat diets (rabbits). Cholesterol fed by itself causes little rise in the serum lipid but fed with lecithin brings about a marked rise. If animals are fed phosphatide there is a protracted post-absorptive hyperlipaemia. Esquimo races do not show abnormally high blood lipid levels.

Diabetics show a hyperlipaemia in spite of high or low fat diets. Pancreatectomy with insulin maintainance tends to cause hypolipaemia with an accumulation of fat in the liver. Raw pancreas administered caused a rise in the blood lipid and drop in liver lipid. Administration of insulin lowers all but the sterol fraction of blood lipids. High carbohydrate diets with low fat content tend to lower fat level of blood and according to Rabinowitch the tendency to hypercholestrolosis of the blood vessels.

Nephrotics fed diets varying from 8-65% fat showed no reliable variation.

In the normal, the fat level of the blood shows a post-prandial rise and then a fall to a starvation level similar to glucose.

From these facts a balanced rather than a low fat diet seems to be indicated.

2. *Is hyperlimpaemia necessary for the development of atherosclerosis?*

In hypertension where atheromatosis is common there is no alteration of any of the significant fractions of the blood lipid from normal. There is no relationship between the serum cholesterol and the incidence of atherosclerosis in autopsy reports on people who died of sudden violence.

3. *Can hyperlipaemia favour atherosclerosis?*

There is a tendency to atherosclerosis in diabetes, nephrosis, Hand-Christian-Schuller syndrome and xanthomatosis.

Diabetics show a raised blood lipid in which the cholesterol portion is increased

proportionately. The amount of cholesterol in the esterified forms is up 10-15% above normal. It has been stated that diabetics with a high cholesterol level are 15 times more likely to develop atherosclerosis than diabetics with a normal blood cholestrol.

Rabbits on a high cholesterol diet develop atherosclerosis. It is uncertain if such occurs in man ; if it does, it must take place over a long period. It is difficult to induce atherosclerosis in rats, dogs and cats (partial carnivors). Rabbits do not metabolise cholesterol as well as vegetable sterols. The mechanism difference appears to be liver function. Cats fed cholesterol show an increase of liver cholesterol by 30-40 times whereas rabbits fed an equivalent amount shows an increase of 6-9 times. This indicates the rabbit liver incapable of retention and therefore the cholesterol goes into general circulation whereas is the cat it is gradually removed to the tissue depots without remarkable blood rise.

4. *Relation of detoxifying ability to atherosclerosis.*

Both herbivorous and carnivorous animals can synthesise cholesterol and it is therefore difficult to estimate destruction rates in terms of ingestion and excretion. Total assay methods indicate that 0.8-1.8 gms/week of cholesterol are destroyed in rats and there is probably a similar figure for rabbits.

5. *Old age and hyperlipaemia.*

In spite of an old contention to the contrary there is no reliable evidence to suggest that there is a physiological hyperlipaemia in old age.

6. *Relation of increased strain on the artery walls.*

Autopsies show that vessels subject to the greatest pressure are most likely to show atheroma. Co-arctation of the aorta causes atheromatous plaques only on the side of the heart. Mechanically fixed arteries show atheroma where arteries in loose tissue do not show such change. Where the arterial pressure is highest, the atheroma is most likely to occur as around the mouths of aortic branches and bifircations.

7. *Other factors.*

(a) Thyroid extract administered concurrently with a high fat diet prevents the development of atheroma.

(b) Potassium iodide also exerted an effect in the prevention of atheroma but was effective only in the presence of the thyroid gland.

(c) Di-iodo-ricinosterolic acid administered had a prolonged preventative effect with few toxic symptoms and this in spite of the fact that the blood lipid was actually raised.

These findings have led to the view that there is some characteristic of the cell involved that decides whether or not an atheromatous plaque will form. It has been found that other substances act similarly such as potassium thiocyanate, silicic acid colloid, garlic oil and lipocaic.

Relation of the atheroma lipid to plasma lipid.

Analysis of plaques show :

1. High cholesterol content.
2. Lipid in the vessel wall in man resembles the lipid in the blood in man. It is also true in some cases in rabbits for high cholesterol diets raise all the plasma lipids.
3. Possibility of change from plasma lipids to plaque lipids.

Klotz suggested that calcification of the plaques was due to separation of the sterols from cholesterol esters deposited

leaving fatty acids in the form of insolube calcium salts; however it has been shown that the calcium shows more the characters of bone than soap. In the early stages the free cholesterol increases. 4. There is a possibility of some breakdown of the cholesterol for a product of similar solubilities can be isolated from the plaques with an absorption band of from 238-320μ which corresponds to cholestenone. Small amounts are found in normal aortas. This does not necessarily indicate active degradation but may indicate selective absorption. Cholestenone may well be an intermediate in cholesterol metabolism for it could readily form a base for cholesterol and coprosterol.

Control of Atherosclerosis.

1. Prevent hyperlipaemia.
2. Prevent great strain on the vessel wall.

Both of these seem to be predisposing causes.

3. Alter the specific receptivity of the cells for lipid.

This is accomplished practically in diabetes where high carboydrate diets and insulin lower the blood lipid to normal levels. Thyroid extract, when tried, has been of inconstant value. The sole effort at prevention of receptivity which has been successful has been in animals but iodide administratiton or some similar treatment may eventually be of value.

H.B.S.

Physiologic Considerations in the Treatment of Portal Cirrhosis

Carl H. Greene, M.D.
J.A.M.A., March 6, 1943

The author presents series of several different authorities in which there is unanimity in setting the age incidence of the disease at 50 (average), the decades of frequency being the 5th and 6th, and the male to female ratio, 3/1. Alcohol is listed variosuly as an antecedent factor in from 38 to 87% of cases; similarly, malnutrition in 17-81%, and syphilis in 16-26%. Symptom frequencies were, abdominal swelling 72-97%, oedema 58-85%, loss of weight 38-78%, dyspepsia 34-54%, haematemsis 15-35%, and pain 21-46%. Clinical signs ran, ascites 64-97%, palpable liver 54.5-84%, palpable spleen 27-70%, jaundice 30-65%, collateral veins 28-76%, and anaemia 21-48%.

A survey is made of the laboratory evidence for pathogensis, the role of chemical agents such as, the chlorinated hydrocarbons (chloroform and carbon tetrachloride especially) phosphorus, arsenic and selenium, tars, and some bacterial infections in the production of cirrhosis being acceptable on both clinical and experimental grounds. Alcohol's part is still indeterminate, but it is significantly noted that fatty infitration and portal cirrhosis is a familiar sequence, and that high fat diet, some cases of diabetes, pancreatectomy (in dogs), and extracts of the anterior pituitary are capable of invoking the same chain of events. And conversely increased amounts of carbohydrate or protein in the diet, or administration of choline, pancreatic extract or lipocaic, will prevent the accumulation of fat and the ultimate development of portal cirrhosis. In this respect yeast has been shown by numerous experimenters to be very efficacious.

Although the relative importance of excess fat and vitamin deficiency in the production of portal cirrhosis is not established, their importance in treatment is, as evidenced by favourable results obtained by Post and Patek, and Fleming and Snell who employ high carbohydrate and protein together with liver extract,

thiamine, and brewers' yeast in the diet. The effects (disappearance of ascites, gain in weight, strength and appetite and increase in serum proteins) are said to be slow to manifest themselves—Patek reports 2 months on the average and Fleming and Snell state that there is little difference in the mortality rates of treated and untreated groups in the first year.

Other phases in the management include the approach to the control of ascites which the author points out is due to 2 factors viz.—portal hypertension and hypoproteinuria, the former being due to interference with blood flow through the liver, the latter to inability of the damaged liver cells to synthesize serum protein (particularly albumen) and to direct loss in the ascitic fluid. The writer finds the use of mercurial diuretics of diminishing efficacity the smaller the difference between the protein concentration of the blood plasma and that of the ascitic fluid, and that the more advanced the cirrhosis the lower the serum proteins and therefore the more ineffective the diuretics late in the disease. Paracentesis of ascitic fluid whose protein content is under 1% does not result in gross protein loss even when considerable quantities are taken. In an attempt to avoid this depletion readministration of the ascitic fluid is used if over 1% protein—the fluid is placed in transfusion bottles in the ice-box for 24 to 72 hours where cells and bits of fibrin are allowed to settle out, the clear fluid is siphoned off and given intravenously at room temperature.

Hyperchromic macrocytic a n a e m i a which develops in severe cases is controlled by liver extract as the liver is no longer able to store the antianaemic principle. Prothrobin time is kept at a normal level with vitamin K. It is mentioned that recently direct injection of oesophogeal varices in an attempt to circumvent haemorrhage has become a heartening possibility.

E.T.F.

Peptic Ulcer at Fort George G. Meade M.D.

Major Chas. A. Flood
Med. Corps, U. S. Army

The author has reviewed 75 cases of peptic ulcer admitted to this military hospital during the year April 1941—April 1942. The delayed response to medical treatment shown by these patients, in contrast to his experience in civilian practise, has prompted him to present this review.

His study was guided by two questions. "Did persistant symptoms signify an actual delay in healing of the peptic ulcer, or were the prolonged symptoms 'functional'?" And secondly, "What was the underlying mechanism for the falure to improve in the way they would under treatment as civilians?"

The material for study comprised 71 duodenal and 4 gastric ulcers. The commonest symptom was persistant moderate epigastric discomfort. The majority of patients were recent recruits, of whom 93% gave histories of symptoms antedating enlistment. Eleven were professional soldiers of long service with recent development of symptoms.

The treatment given as outlined later, consisted of partial rest, diet, alkalis and anti-spasmodics, varying with severity of symptoms.

One third of patients were relieved of symptoms within two weeks. One half continued to have pain for four weeks. The average hospitalization time was two months.

St. John and Flood in a study of 225 civilian duodenal ulcer cases reported two thirds with complete symptomatic relief

in two weeks. Immediate relief was commonly observed during the first day in hospital. Such was observed in only four of the Fort George G. Meade Series.

Roentgen examination was carried out on three of the gastric ulcers. After six weeks of treatment the craters appeared undiminished in size. In civilian practise Jordan states 90% gastric ulcers disappear completely in eight weeks of treatment, judged by roentgen examination.

Delayed healing was demonstrated in duodenal ulcers as well. Unimproved craters were seen after two weeks treatment in 50% of patients who showed ulcers originally. Only a small minority of civilians show failure to improve after a similar period of treatment.

Forty-seven patients were studied from the neuro-psychiatric view point. Twenty-five presented symptoms of an anxiety state, causes of worry being health and inability to adjust to army life. Symptoms always persisted until discharge from the army was assured. Of this group of 25 only 4 obtained complete relief after two weeks treatment. Of the 22 regarded stable personalities, 13 experienced such relief in the same period. Of the 11 professional soldiers, 7 obtained complete relief in less than one week.

Commenting, the author points out that response to treatment in the army was unsatisfactory by civilian standards. Roentgen studies show actual delay in healing, and protracted symptoms were often associated with obvious anxiety states. He suggests the latter as the cause of the delayed healing.

In conclusion the author advises the following treatment for use in station hospitals:

The objectives are, 1. Prompt diagnosis. 2. Relief of symptoms and healing of the ulcer. 3. Early classification either for return to active duty, or for discharge from the army.

The treatment is:

1. Establish a diagnosis by two roentgen examinations three weeks apart.
2. A three weeks regimen of rest, frequent feedings, alkalis, anti-spasmodics in full physiological doses, and psychotherapy.
3. Necessary discharges should be put through as rapidly as possible. This will save many days in hospital.
4. For soldiers eligible for return to duty, after complete symptomatic and roentgen cure, a trial diet is provided, consisting of regular mess hall food. If unable to tolerate such a diet, the patient is unfit for active service.
5. Before return to active duty, patients should be given a complete neuropsychological appraisal. Only stable personalities should be passed for active duty.
6. All soldiers retained in service should be reclassified for limited duty.

C.M.W.

The Rh Factor in Relation to Jaundice of the New-Born Infant (Erythroblastosis Fetalis)

Fred W. Gallagher, Ph.D., Peter G. Danis, M.D., Lloyd R. Jones, Ph.D.
Journal of Pediatrics, Feb. '43

Levine and co-workers have advanced the theory that the Rh antibody-antigen mechanism is an etiological factor in erythroblastosis fetalis in which an Rh negative mother carries an Rh positive fetus in her uterus. This theory holds that fetal blood enters the maternal circulation through some break in the placental barrier and produces antibodies in the mother which diffuse back and destroy the fetal erythrocytes. It is also thought that erythroblastosis fetalis is

only one clinical aspect of a syndrome made up of fetal hydrops, icterus gravis neonatorum and anemia of the newborn.

The writers of this paper have tested the blood of mothers and of infants who showed signs of the above syndrome. They tested particularly for Rh antigen and its corresponding antibody. In their series of twenty mothers 11 were Rh negative and 9 were Rh positive and so 43% of the cases cannot have an antigen-antibody relationship as the bases for the erythroblastosis. This finding varies with that of Levine who reported 90% of mothers of erythroblastic infants were Rh negative.

It was also found that the presence or absence of demonstrable antibody bore no relationship to the severity of the disease. The authors therefore conclude that it is impossible to regard the Rh antigen-antibody mechanism as the only etiologic factor in this syndrome and that the diagnosis of erythroblastosis by the determination of the Rh status of mother and infant is of limited value.

J.S.S.

The $500 Research Prize annually offered by the American Urological Association will not be awarded this year.

The Government has again discouraged the holding of medical conventions, except those primarily of military interest—and at these there is to be a ban on social events. Under the circumstances, plans for the June meeting of the American Urological Association in St. Louis have been cancelled

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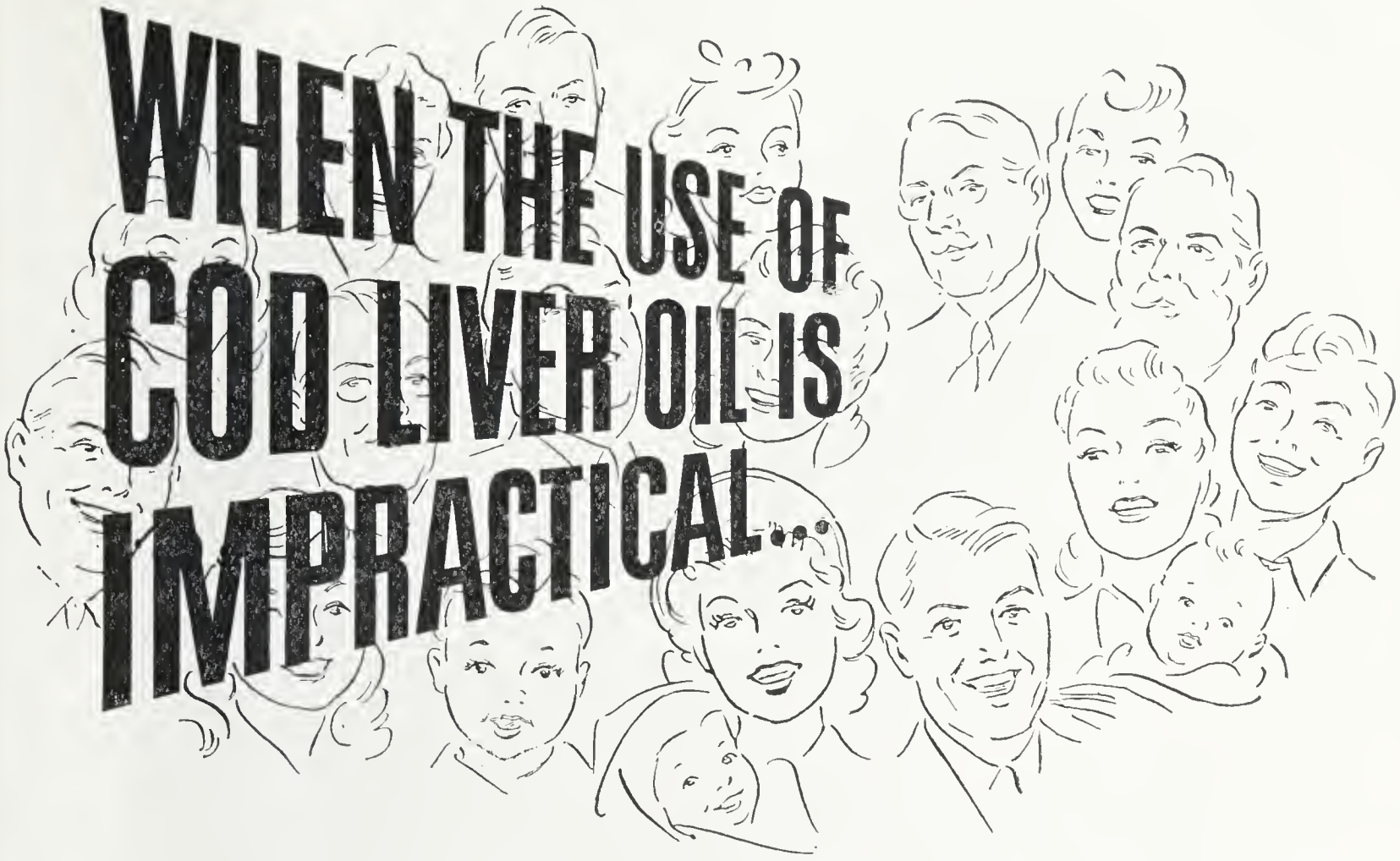

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The subjects of the Primary Examination are:—Anatomy, including Histology and Embryology; Physiology, including Biochemistry.

The Primary Examination is partly written and partly oral and must be passed as a whole.

The Primary Examination may be taken at any time after the candidate has completed a course of study and passed the examinations, in Anatomy, Histology, Embryology, Physiology, and Biochemistry, in a Medical School or University approved by Council. The candidate must submit a certificate thereof with his application.

LANGUAGES OF EXAMINATION

Candidates at the time of making application for either the Primary or the Final Examination shall indicate whether they desire to be examined in the French or English language.

STANDARDS OF QUALIFICATION

No particular list of text books or syllabus is recommended to cover any subject. All candidates are expected to demonstrate a thorough knowledge of the subjects in which they are to be examined and to be familiar with the current literature relating thereto.

In their answers, written or oral, candidates in the Final Examination must show evidence of critical judgement.

PLACES AND DATES OF EXAMINATIONS—1943

The Centres selected for the Written Examinations are Vancouver, Edmonton, Saskatoon, Winnipeg, London, Toronto, Kingston, Montreal, Quebec, and Halifax.

SPECIAL Primary Examination—May 31st and June 1st.
Annual Examinations —Oct. 4th, 5th, and 6th.

Oral Examinations in the Primary subjects and Oral and Clinical Examination in the Final subjects will be held as follows:

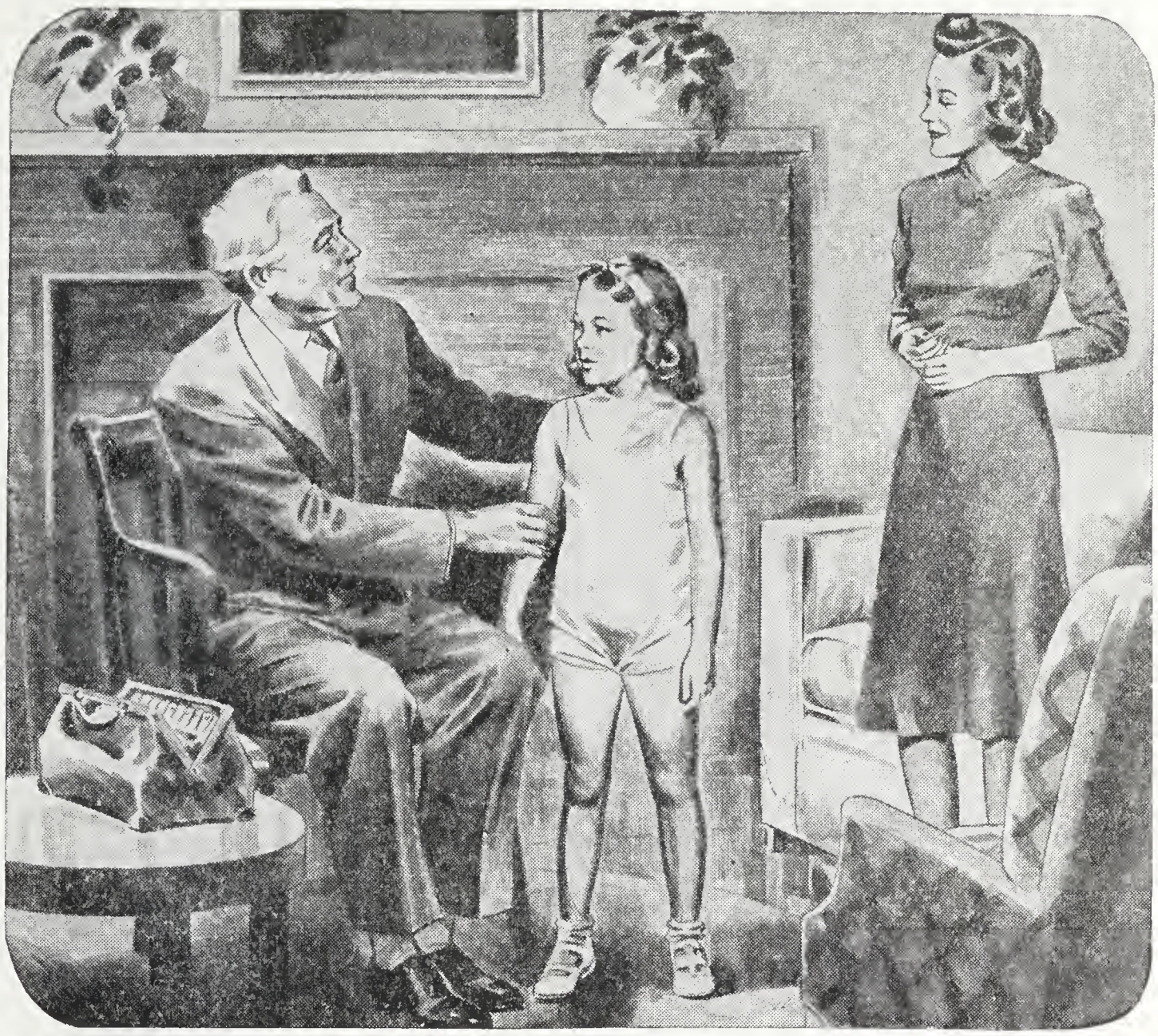
SPECIAL Primary Examination—at Montreal—June 15th.
Annual Examinations —at Toronto—October 25th and 26th.

Candidates who are graduates of 1930 or prior thereto of a Medical School or University approved by Council shall not be required to take the Primary Examination, but shall in the Final Examination demonstrate a general and practical knowledge of the clinical application of Anatomy and Physiology.

This special examination shall be conducted by Clinicians.

Address all communications to—

Warren S. Lyman, M.D., F.R.C.P.(C.),
Honorary Secretary,
Room 3018, National Research Laboratories,
Sussex Street, Ottawa, Ontario.



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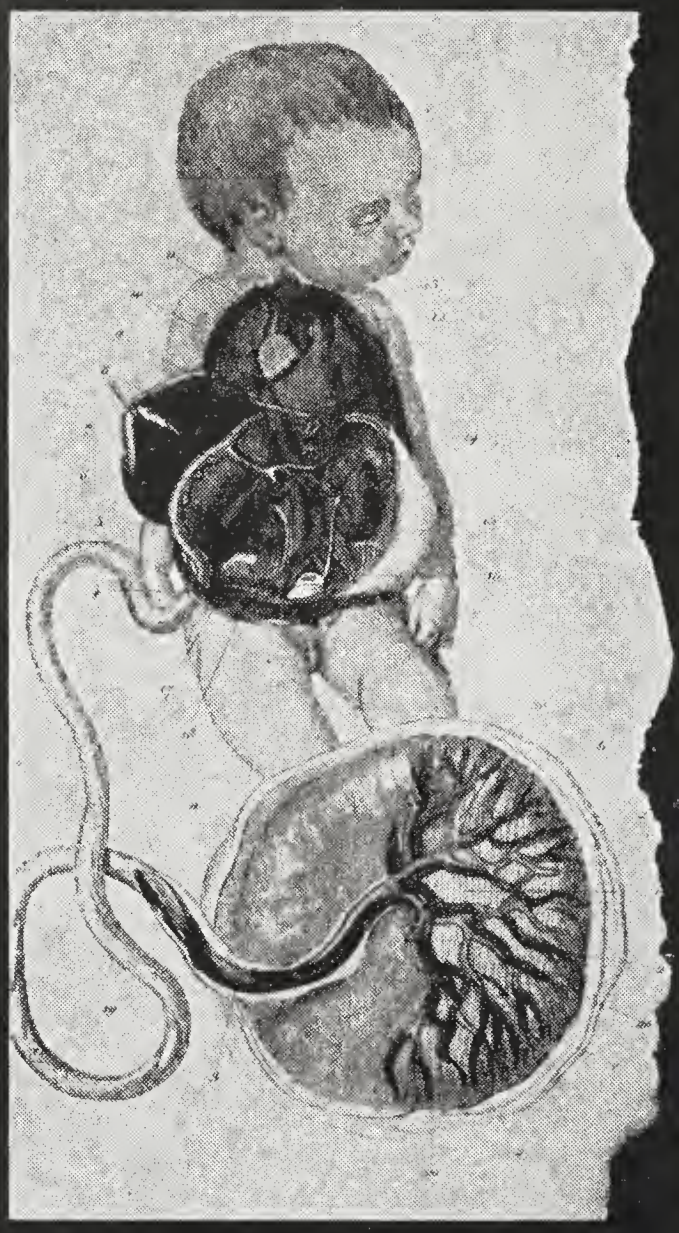
(1) 1939, U. S. Dept. Commerce, Bureau of Fisheries Investigational Report No. 41



This interesting study of fetal circulation is taken from Antonin Bossu's Anthropologie Etude des Organes, Fonctions, Maladies de l'Homme et de la Dame published in Brussels in 1847.

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